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# BMJ Open

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**The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study**

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## Abstract

**Objectives:** Recent studies reported that 24-hour ambulatory blood pressure variability (ABPV) was associated with lacunar brain infarction and white matter hyperintensities (WMH). However, the relationship between ABPV and enlarged perivascular spaces (EPVS) hasn't been investigated. So in the study, we aimed to investigate whether ABPV was associated with EPVS by 24-hour ambulatory blood pressure monitoring (24h ABPM).

**Design:** We conducted this study as a cross-sectional study.

**Settings:** The study was based on patients for physical examinations in our hospital from May 2013 to Jun 2016.

**Participants:** Patients with both brain MRI scans and 24h ABPM were included and patients with acute stroke, a history of severe stroke and some other severe diseases were excluded. A total of 573 Chinese were prospectively enrolled in this study.

**Primary and secondary outcome measures:** EPVS in basal ganglia (BG) and white matter (WM) were identified on MRI and classified into three categories by the severity. WMH were scored by Fazekas scale. Spearman correlation analysis and multivariate logistic regression analyses were used to determine the relationship between ABP levels and EPVS.

**Results:** There were statistical differences in all of the following ABPV metrics: 24h, daytime, nighttime systolic blood pressure standard deviation (SBP-SD), systolic blood pressure coefficient of variation (SBP-CV) and diastolic blood pressure coefficient of variation (DBP-CV) and nighttime DBP-SD among the three subgroups stratified by EPVS severity in BG ( $p < 0.05$ ). The above ABPV metrics were linearly associated with the degree of EPVS in BG by spearman correlation analysis. The association between ABPV and EPVS in BG was unchanged after controlling for confounders. The results of spearman correlation analysis showed ABPV weren't related to the degree of EPVS in WM.

**Conclusion:** ABPV was linearly associated with EPVS in BG, but not in WM. Pathogenesis of EPVS in BG and WM may be different.

**Keywords** cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

**Strengths and limitations of this study**

- Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments.
- Detailed information on some confounders crucial to the interpretation of EPVS was collected and multivariate logistic regression analyses were performed to determine the independency of association.
- The study was based on hospital physical examinations people in a single center and the cohort may not represent the general population.
- This was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established.

**INTRODUCTION**

Perivascular spaces, or Virchow-Robin spaces, are perivascular compartments surrounding the small penetrating cerebral vessels, serving as an important drainage system for interstitial fluid and solute in brain<sup>1</sup>. They can dilate with accumulation of the interstitial fluid<sup>2, 3</sup>. Enlarged perivascular spaces (EPVS) appear as punctate or linear signal intensities similar to cerebrospinal fluid (CSF) on all MRI sequences in white matter (WM), basal ganglia (BG), hippocampus and brainstem<sup>4, 5</sup>. Recent studies indicated that EPVS were a magnetic resonance imaging (MRI) marker of cerebral small vessel diseases (CSVD) and were associated with other morphological features of CSVD such as white matter hyperintensities (WMH) and lacunes<sup>6, 7</sup>. Some studies found EPVS were associated with impaired cognitive function<sup>5</sup>, incident

dementia<sup>8</sup> and sleep disorders<sup>9</sup>. Therefore, it is of clinical importance to understand the risk factors of EPVS and search for treatable methods.

24-hour ambulatory blood pressure monitoring (24-h ABPM) is proven to be a more useful and scientific method to predict blood pressure-related brain damage than single office blood pressure measurements<sup>10, 11</sup>. Ambulatory blood pressure variability (ABPV) could be well documented by 24-h ABPM. Previous studies demonstrated higher ABPV increased the risk of cardiovascular events<sup>12, 13</sup>, WMH, lacunar infarction, and cognitive decline<sup>14, 15</sup>. WMH, lacunar infarction and EPVS are all neuroimaging features of CSVD and share some risk factors, such as age and hypertension<sup>16</sup>. However, the relationship between ABPV and EPVS has never been investigated. So in the study, we aimed to investigate whether ABPV was associated with EPVS by 24-h ABPM.

## METHODS

### Study subjects

We conducted this study as a cross-sectional study. The patients meeting both inclusion and exclusion criteria for physical examinations were prospectively enrolled to avoid selection bias in Beijing Chaoyang Hospital Affiliated to Capital Medical University from May 2013 to Jun 2016. The number of arriving patients during the study period, inclusion and exclusion criteria determined the sample size. Inclusion criteria were: (1) patients undergo brain MRI scans; (2) patients undergo 24-h ABPM; (3) the interval of brain MRI scans and 24-h ABPM was less than 1 month; (4) patients agreed to participate in our study and sign an informed consent. The following patients were excluded: (1) patients with acute stroke, Parkinson disease, dementia, severe traumatic or toxic or infectious brain injury, and brain tumor; (2) patients with severe heart disease, recent myocardial infarction or angina pectoris disorders, severe infections, severe nephrosis or liver disease, thrombotic diseases and tumor; (3) patients with history of severe ischemic (the largest diameter of infarct size >20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke because of difficulty assessments on EPVS; (4) patients with

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invalid 24-h ABPM data (The 24-h ABPM data were considered invalid if measurement was < 70%, < 1 measurement per hour during daytime, and < 6 in total during nighttime).

**Assessments of EPVS and WMH**

The neurological image examinations were performed in Radiology Department of Beijing Chaoyang Hospital Affiliated to Capital Medical University. MR imagings were acquired on 3.0 T Siemens scanner (Erlangen, Germany). Assessments of EPVS and white matter hyperintensitis (WMH) were performed by two experienced neurologists blinded to clinical information to avoid bias. Disagreements were resolved by consensus.

EPVS were defined as CSF-like signal intensity lesions of round, ovoid, or linear shape of <3mm and located in areas supplied by perforating arteries<sup>6, 17</sup>. We distinguished lacune from EPVS by their larger size (>3mm), spheroid shape and surrounding hyperintensities on FLAIR. WMH were defined as hyperintense signals on T2-weighted and FLAIR and decreased signal intensities on T1-weighted MR imaging.

EPVS in BG and WM were separately assessed according to the scales which were used in other studies<sup>18, 19</sup>. In BG, EPVS were rated according to the number in the slice containing the maximum amount of EPVS. The grades of EPVS were rated as follows: grade 1: < 5 EPVS, grade 2: 5 to 10 EPVS, grade 3: > 10 but still countable, and grade 4: infinite number of EPVS. In WM, EPVS were scored as follows: grade 1: <10 EPVS in total WM, grade 2: >10 in total WM and <10 in the slice containing the maximum number of EPVS, grade 3: 10 to 20 EPVS in the slice containing the

maximum number of EPVS, grade 4: > 20 in the slice containing the maximum number of EPVS. We classified EPVS into three categories: degree 1 = grade 1; degree 2 = grade 2; degree 3 = grade 3 or 4.

WMH were scored by Fazekas scale. The detailed description of assessment has been previously published<sup>20</sup>. Periventricular and deep WMH were evaluated separately and totaled together as Fazekas scores.

### **24-hour ambulatory blood pressure monitoring**

24-h ABPM was performed using an automated system (FB-250; Fukuda Denshi, Tokyo, Japan). BP was measured every 30 minutes during the daytime (8:00 AM to 11:00 PM) and every 60 minutes during the nighttime (11:00 PM to 8:00 AM). We excluded a 2-hour transition period around the reported rising and retiring times. Mean 24-h, daytime, and nighttime systolic and diastolic blood pressure coefficient of variation (CV) and standard deviation (SD) were collected. The CV value was defined as the ratio between the SD and the mean systolic blood pressure (SBP) or diastolic blood pressure (DBP) at the same periods. SD and CV were considered as metrics of BPV in this study. Patients continued their previous medication, and we registered the use of anti-hypertension drugs.

### **Statistical analysis**

Continuous variables were presented as mean values  $\pm$  SD and compared with ANOVA for factors with a normal distribution, whereas no normally distributed variables were compared with Kruskal–Wallis test as appropriate. Categorical variables were expressed as percentages and compared using the chi-square test.



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Spearman correlation analysis was used to calculate the association between ABPV and the severity of EPVS. In addition, multivariate logistic regression analyses were performed to determine whether the ABPV were independently associated with EPVS after adjustment for other confounders. The results were based on valid data; missing data were excluded. Analyses were performed with Statistical Package for Social Sciences (SPSS version21.0), and statistical significance was accepted at the  $p < 0.05$ .

**RESULTS**

**Baseline characteristics of the study participants**

742 patients undergo both brain MRI scans and 24-h ABPM within 1 month in Beijing Chaoyang Hospital Affiliated to Capital Medical University from May 2013 to Jun 2016. 40 patients were excluded because of acute stroke, 21 were excluded because of history of severe or hemorrhagic stroke, 15 were excluded because of a history of tumor and 93 were excluded because of invalid ABPM data, leaving 573 patients for the present study. None of them had missing data. Table 1 showed the characteristics of all subjects and different subgroups stratified by EPVS severity in BG and WM. Age, Fazekas scale, proportion of hypertension and stroke/TIA, levels of blood urea nitrogen and creatinine increased with the degree of EPVS in BG increasing. There were statistical differences in age, Fazekas scale and proportion of coronary artery atherosclerosis disease (CAD) among subgroups based on EPVS degree in WM.

**Table 1.** General characteristics of all subjects and subgroups stratified by EPVS severity

Characteristics	All patients	EPVS in BG			EPVS in WM		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3
n	573	244	179	150	200	207	166
Age, years	67.8±14.8	61.4±14.4**	67.6±13.8**	78.3±9.6**	70.45±15.2**	66.25±14.4**	66.46±14.3**
Sex, male (%)	355 (62.0)	143 (58.6)	108 (60.3)	104 (69.3)	115 (57.5)	128 (61.8)	112 (67.5)
Current smoking (%)	162 (28.3)	83 (34.0)*	61(34.1)*	18(12.0)*	52 (26.0)	60 (29.0)	50 (30.1)
Current alcohol (%)	126 (22.0)	62 (25.4)*	45 (25.1)*	19 (12.7)*	36 (18.0)	50 (24.2)	40 (24.1)
Hypertension (%)	420 (73.3)	170 (69.7)*	122 (68.2)*	128 (85.3)*	150 (75.0)	145 (70.5)	125 (74.7)
Diabetes (%)	191 (33.3)	78 (32.0)	59 (33.0)	54 (36.0)	71 (35.5)	62 (30.0)	58 (34.9)
CAD (%)	140 (24.4)	48 (19.7)	48 (26.8)	44 (29.3)	61 (30.5) *	45 (21.7) *	34 (20.5) *
Stroke or TIA (%)	125 (21.8)	40 (16.4)**	33 (18.4)**	52 (34.7)**	49 (24.5)	39 (18.8)	37 (22.2)
BMI, kg/m <sup>2</sup>	25.6±3.5	25.6±3.4	25.3±3.5	25.8±3.5	25.8±3.4	25.4±3.5	25.5±3.5
HDL, mmol/L	1.2±0.4	1.2±0.4	1.2±0.4	1.2±0.3	1.2±0.4	1.2±0.4	1.2±0.3
LDL, mmol/L	2.5±0.8	2.5±0.8	2.5±0.8	2.3±0.8	2.4±0.8	2.4±0.8	2.5±0.7
HbA1c, %	6.4±1.3	6.4±1.3	6.4±1.4	6.5±1.2	6.4±1.1	6.5±1.4	6.5±1.4
BUN, mmol/L	5.8±2.1	5.5±1.7**	5.9±2.6**	6.3±2.0**	6.0±2.5	5.7±1.9	5.8±1.9
Creatinine, umol/L	79.1±27.1	74.0±19.3**	81.7±32.6**	84.2±29.4**	81.2±27.4	77.7±27.3	78.3±26.4
Fazekas scale	3.1±1.8	2.2±1.4**	3.1±1.7**	4.7±1.5**	3.5±2.0**	2.9±1.7**	3.1±1.7**
Using of anti-hypertensive drugs (%)	342 (59.7)	130 (53.3) *	96 (53.6) *	116 (77.3) *	129 (64.5)	114 (55.1)	99 (59.6)

EPVS, enlarged perivascular spaces; BG, basal ganglia; WM, white matter; BMI, body mass index; CAD, coronary artery atherosclerosis disease; TIA, transient ischemic attack; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen. \*  $p < 0.05$ , \* \*  $p < 0.01$ .

### Association between ABPV and EPVS in BG

Ambulatory blood pressure SD and CV of EPVS in BG were presented in Table 2.

There were statistical differences ( $p < 0.05$ ) in all of the following BPV metrics: 24h,

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daytime, nighttime SBP-SD, SBP-CV, DBP-CV and nighttime DBP-SD among the three subgroups stratified by EPVS severity in BG. In addition, these metrics gradually increased with the degree of EPVS increasing (Fig 1-3). The results of spearman correlation analysis demonstrated these metrics were linearly associated with the degree of EPVS in BG (Table 3). The association between ABPV and EPVS were unchanged after controlling for demographic confounders (model 1) and Fazekas scale (model 2). The results of multiple logistic regression analysis were presented in Table 4.

**Association between ABP Levels and EPVS in WM**

Ambulatory blood pressure SD and CV of EPVS in WM were also presented in Table 2. There were statistical differences ( $p < 0.05$ ) in 24h and daytime SBP-SD, DBP-SD, SBP-CV and DBP-CV among the three subgroups stratified by EPVS severity in WM. However, there were not linear trend among the three subgroup stratified by EPVS severity. The results of spearman correlation analysis showed there were no linear correlation between these metrics and the degree of EPVS in WM (Table 3).

**Table 2.** Results of ABPV in all subjects and subgroups stratified by EPVS severity

	All patients	EPVS in BG			EPVS in WM		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3
24h							
SBP-SD, mmHg	18.28±5.27	16.93±4.76**	18.57±4.56**	20.13±6.21**	18.86±5.56**	17.36±5.11**	18.73±4.99**
DBP-SD, mmHg	12.56±3.58	12.22±3.56	12.62±3.34	13.05±3.86	12.83±3.76**	11.85±3.32**	13.14±3.56**
SBP-CV, %	13.83±3.80	13.21±3.56**	13.99±3.54**	14.64±4.26**	14.16±3.87*	13.23±3.70*	14.18±3.76*

DBP-CV, %	16.68±4.74	16.03±4.68*	16.82±4.46*	17.55±5.04*	17.22±4.76**	15.78±4.72**	17.14±4.60**
Daytime							
SBP-SD, mmHg	18.02±5.70	16.66±4.93**	18.21±5.35**	19.99±6.65**	18.68±5.98**	16.99±5.47**	18.50±5.49**
DBP-SD, mmHg	12.56±4.01	12.25±3.80	12.51±3.93	13.12±4.40	12.81±4.06**	11.76±3.71**	13.26±4.17**
SBP-CV, %	13.45±4.08	12.84±3.75**	13.62±4.14**	14.26±4.38**	13.86±4.16*	12.76±3.88*	13.81±4.12*
DBP-CV, %	16.48±5.19	15.84±4.77*	16.47±5.24*	17.54±5.63*	16.98±4.88**	15.47±5.12**	17.15±5.48**
Nighttime							
SBP-SD, mmHg	15.21±7.37	13.79±7.71**	15.18±5.74**	17.54±7.97**	15.08±6.09	14.94±8.66	15.69±7.05
DBP-SD, mmHg	10.43±4.50	9.81±4.33*	10.77±4.55*	11.03±4.61*	10.23±4.11	10.26±4.58	10.88±4.84
SBP-CV, %	11.85±5.37	11.22±5.53**	11.77±4.56**	12.95±5.84**	11.69±4.62	11.70±5.95	12.23±5.48
DBP-CV, %	14.26±6.02	13.42±5.88**	14.75±5.89**	15.03±6.28**	14.20±5.61	14.08±6.30	14.54±6.17

SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of variation; SD: standard deviation. \*  $P < 0.05$ , \*\*  $P < 0.01$ .

**Table 3.** Results of spearman correlation analyses between the degree of EPVS and ABPV

	EPVS in BG		EPVS in WM	
	r	P value	r	P value
24h				
SBP-SD	0.216	0.000	-0.013	0.762
DBP-SD	0.082	0.051	0.030	0.481
SBP-CV	0.137	0.001	-0.008	0.854
DBP-CV	0.123	0.003	-0.028	0.505
Daytime				
SBP-SD	0.205	0.000	-0.024	0.562

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DBP-SD	0.065	0.120	0.031	0.459
SBP-CV	0.135	0.001	-0.023	0.585
DBP-CV	0.109	0.009	-0.017	0.679
Nighttime				
SBP-SD	0.229	0.000	0.020	0.637
DBP-SD	0.125	0.003	0.043	0.309
SBP-CV	0.136	0.001	0.027	0.521
DBP-CV	0.135	0.001	0.007	0.870

SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of variation; SD: standard deviation.

**Table 4.** Results of multivariate logistic regression analyses between ABPV and EPVS in BG (Degree 3 vs. Degree 1)

	Model 1		Model 2	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
24h				
SBP-SD	1.135(1.081, 1.191)	0.000	1.129(1.070, 1.191)	0.000
SBP-CV	1.121(1.052, 1.194)	0.000	1.138(1.060, 1.222 )	0.000
DBP-CV	1.075(1.022, 1.130)	0.005	1.091(1.031, 1.154)	0.002
Daytime				
SBP-SD	1.110(1.063, 1.160)	0.000	1.109(1.057, 1.164)	0.000
SBP-CV	1.083(1.022, 1.147)	0.007	1.096(1.028, 1.169)	0.005
DBP-CV	1.069(1.021, 1.119)	0.005	1.088(1.035, 1.145)	0.001
Nighttime				
SBP-SD	1.071(1.034, 1.108)	0.000	1.062(1.025, 1.101)	0.001
DBP-SD	1.102(1.044, 1.163)	0.000	1.096(1.034, 1.161)	0.002
SBP-CV	1.073(1.027, 1.121)	0.002	1.076(1.027, 1.127)	0.002
DBP-CV	1.052(1.012, 1.094)	0.011	1.060(1.015, 1.106)	0.008

Results of multiple regression analyses presented as OR per 1% increase in BP-CV and 1mmHg in BP-SD

Reference group: degree 1 subgroup of EPVS in BG.

Model1: adjusted for age, smoking, alcohol, hypertension, stroke/TIA, BUN and creatinine and using of anti-hypertensive drugs.

Model2: model 1 + Fazekas scale.

## DISCUSSION

In this study, we explored the relationship between ABPV and EPVS based on hospital physical examinations population. Our data suggested that all of the following metrics: 24h, daytime and nighttime SBP-SD, SBP-CV and DBP-CV were linearly associated with the degree of EPVS in BG. The association between the above ABPV metrics and EPVS in BG were unchanged after controlling for demographic confounders and Fazekas scale. Although there were statistical differences in 24h and daytime ABPV metrics among the three subgroups stratified by EPVS severity in WM, there were not linear correlation between ABPV and the degree of EPVS in WM. In addition, we found age, Fazekas scale, hypertension, stroke/transient ischemic attack (TIA), levels of blood urea nitrogen and creatinine were positively associated with the degree of EPVS in BG.

There were methodological strengths of our study. We recruited participants strictly according to inclusion and exclusion criteria to avoid selection bias. In addition, assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which

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ensure the accuracy of the assessments. We collected detailed information on vascular confounders, WMH, levels of blood urea nitrogen and creatinine, which are crucial to the interpretation of EPVS<sup>6, 21</sup>. So we think the reliability of the data is high. There were some limitations in our study. First, our study was based on hospital physical examinations people in a single center and the cohort may not represent the general population. Second, this was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established. Third, all participants undergo 24h ABPM which could only show short-term ABPV. It has been demonstrated that the prognostic significance of BPV on vascular diseases is weaker for short-term than for long-term BPV<sup>22</sup>.

This is the first study to investigate the relationship between ABPV and EPVS. Previously, several studies investigated the relationship between EPVS and hypertension. In a prospective, multicenter, hospital-based study, Zhang CQ et al<sup>19</sup> found hypertension was associated with the severity of EPVS in WM, not in BG. Pim K et al<sup>23</sup> investigated the association between ABP levels and EPVS in first-ever lacunar stroke patients. Their study found higher day systolic, day diastolic and 24-h diastolic ABP levels were independently associated EPVS in BG, and no relation between ABP levels and EPVS in WM. Our data suggested that 24h, daytime and nighttime SBP-SD, SBP-CV and DBP-CV were linearly associated with the degree of EPVS in BG, but not in WM. The present study couldn't explain the phenomenon. This may be caused by different pathogenesis of EPVS at the different locations. Previous studies have demonstrated higher ABPV increased the risk of neuroimaging

features of CSVD, such as WMH and lacunar infarction<sup>14, 15</sup>. Our results found higher ABPV was independently with higher degree of EPVS in BG, which support the notion that EPVS in BG are a separate marker of CSVD.

An increased permeability of the small vessel walls and blood brain barrier (BBB) are considered to contribute to the development of EPVS, which has been reported to be associated with damage of microvascular endothelial cells and their tight junctions<sup>1, 16, 24</sup>. Higher ABPV would lead to more mechanical stress on the wall vessel, endothelial injury<sup>25</sup> and arterial stiffness<sup>26</sup>. So, it is reasonable that high ABPV contribute to the development of EPVS by the damage to endothelial cell. Our results may remind clinicians that reducing patients' ABPV is as important as reducing patients' high blood pressure levels. In the future, the causal relationship between ABPV and EPVS should be established in a cohort study. And the relationship between ABPV and EPVS should be explored.

## CONCLUSION

24h, daytime and nighttime SBP-SD, SBP-CV and DBP-CV were linearly associated with the degree of EPVS in BG. The association was unchanged after controlling for confounders. No relation was found between ABPV and EPVS in WM. It is important for clinicians to reduce both patients' high blood pressure levels and ABPV.

**Contributors** WH conceived and designed the experiments. SY, WQ, LY and HF participated in the data collection. JY and YL participated in the analysis of the data. SY drafted the manuscript. WH has given final approval of the version to be published. All authors read and approved the final manuscript.



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**Conflict of Interest** None declared.

**Ethic approval** The study was approved by the Ethics Committee of Beijing Chaoyang Hospital Affiliated to Capital Medical University and was performed in accordance with the declaration of Helsinki.

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**Data sharing statement** No additional data are available.

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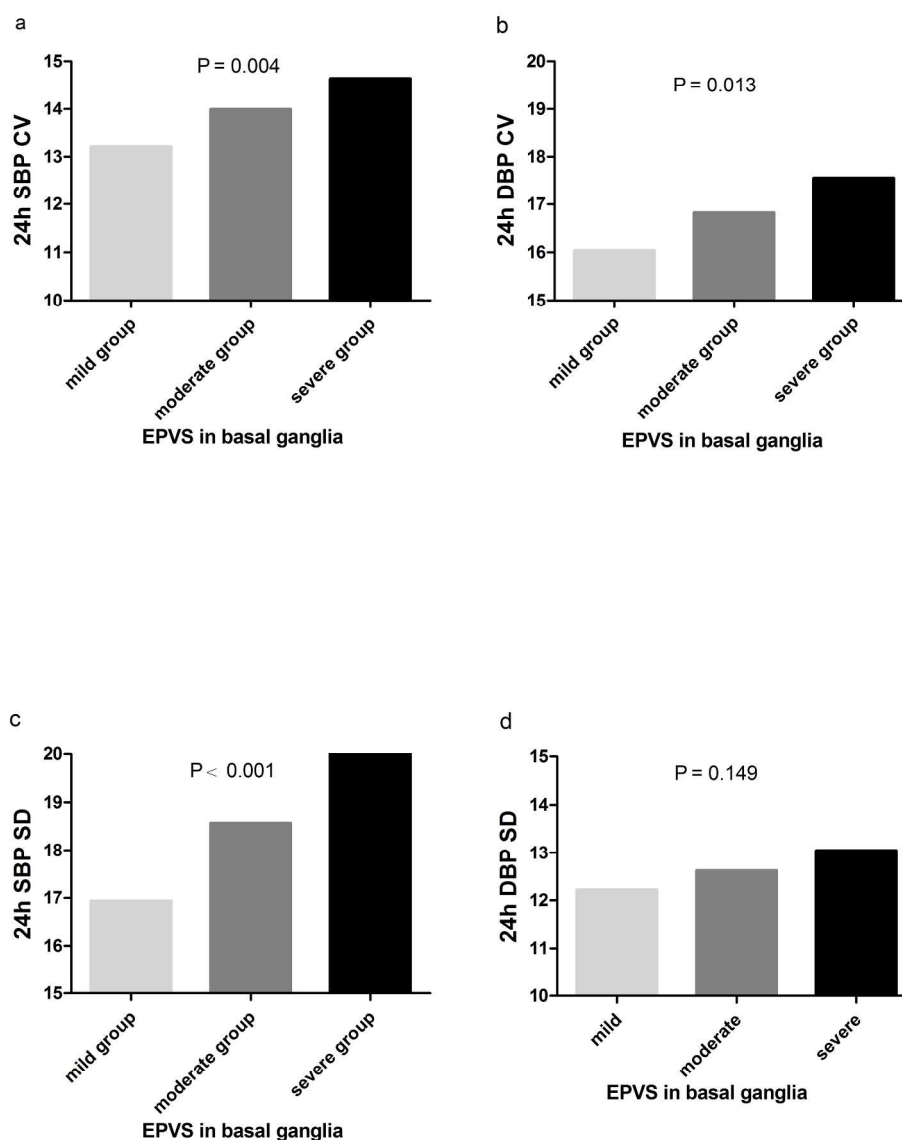


Figure 1. 24h mean ABPV metrics of subgroups stratified by EPVS severity in BG. (a) CV of 24h mean systolic blood pressure. (b) CV of 24h mean diastolic blood pressure. (c) SD of 24h mean systolic blood pressure. (d) SD of 24h mean diastolic blood pressure.

237x292mm (300 x 300 DPI)

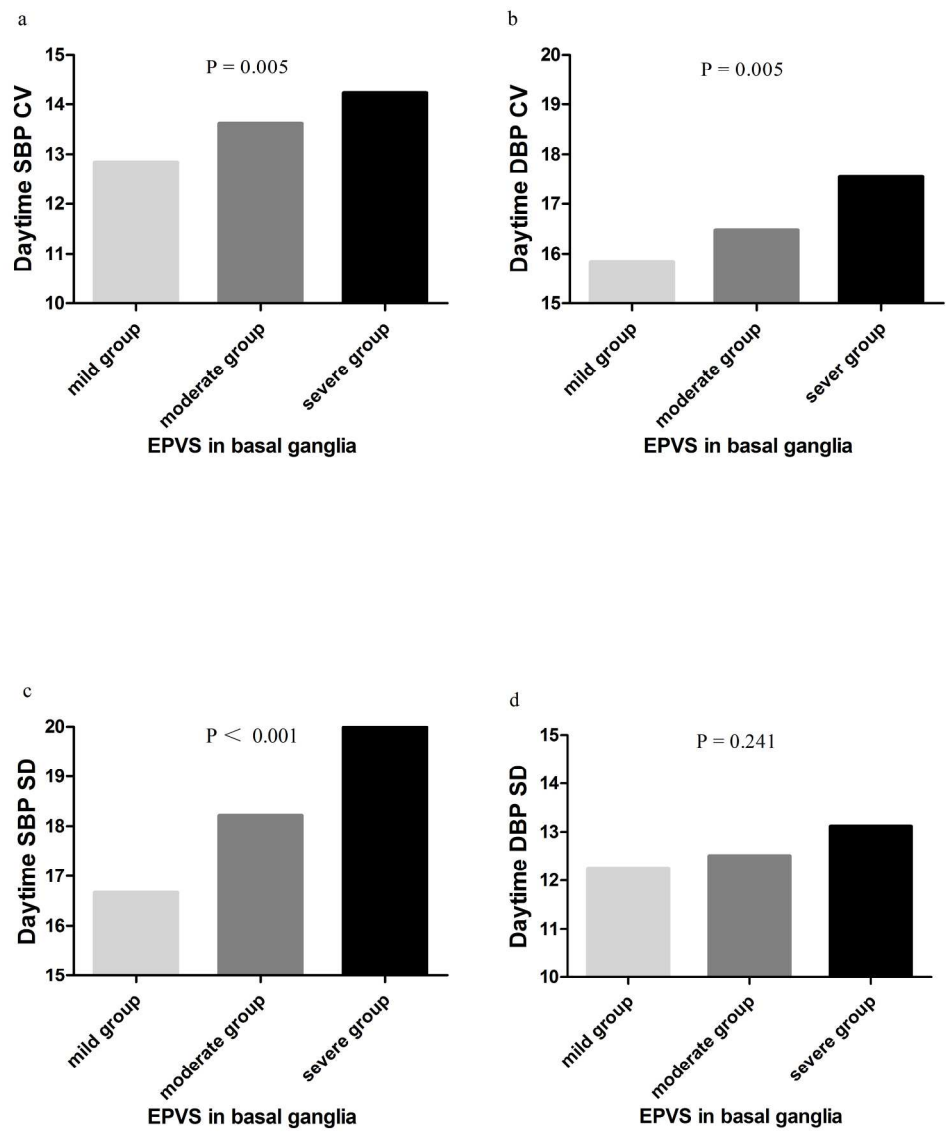


Figure 2. Daytime mean ABPV metrics of subgroups stratified by EPVS severity in BG. (a) CV of daytime mean systolic blood pressure. (b) CV of daytime mean diastolic blood pressure. (c) SD of daytime mean systolic blood pressure. (d) SD of daytime mean diastolic blood pressure.

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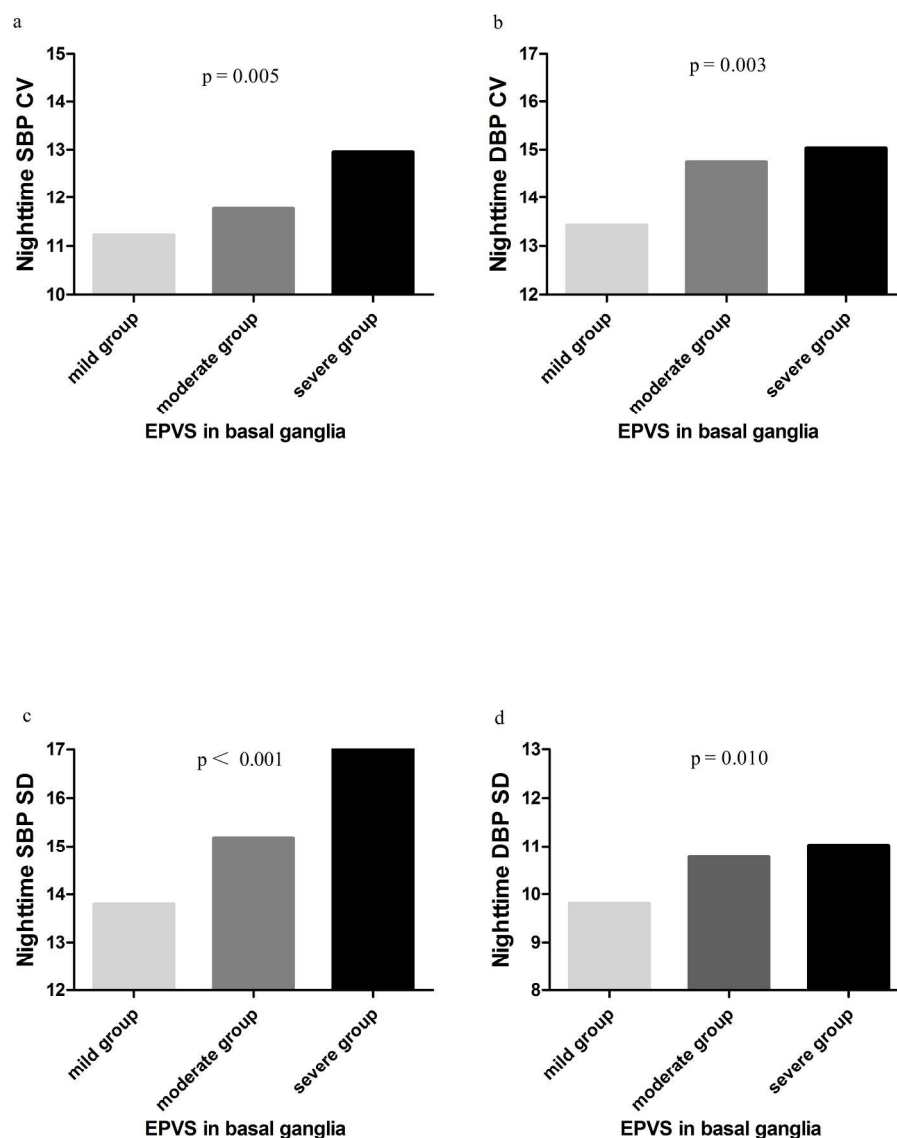


Figure 3. Nighttime mean ABPV metrics of subgroups stratified by EPVS severity in BG. (a) CV of nighttime mean systolic blood pressure. (b) CV of nighttime mean diastolic blood pressure. (c) SD of nighttime mean systolic blood pressure. (d) SD of nighttime mean diastolic blood pressure.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	P1 and 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	P2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	P4
Methods			
Study design	4	Present key elements of study design early in the paper	P4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	P4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P5-6
Bias	9	Describe any efforts to address potential sources of bias	P4 and 5

Study size	10	Explain how the study size was arrived at	P4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	P6-7
		(b) Describe any methods used to examine subgroups and interactions	P6-7
		(c) Explain how missing data were addressed	P7
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P7
		(b) Give reasons for non-participation at each stage	P7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P7-8
		(b) Indicate number of participants with missing data for each variable of interest	P7
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P9-12
		(b) Report category boundaries when continuous variables were categorized	



		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	P12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	P15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P15

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

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## The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

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**The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study**

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## Abstract

**Objectives:** Recent studies reported that 24-hour ambulatory blood pressure variability (ABPV) was associated with lacunar infarction and white matter hyperintensities (WMH). However, the relationship between ABPV and enlarged perivascular spaces (EPVS) hasn't been investigated. So in the study, we aimed to investigate whether ABPV was associated with EPVS by 24-hour ambulatory blood pressure monitoring (ABPM).

**Design:** We conducted this study as a cross-sectional study.

**Settings:** The study was based on patients for physical examinations in our hospital from May 2013 to Jun 2016.

**Participants:** Patients with both brain MRI scans and 24-hour ABPM were included and patients with acute stroke, a history of severe stroke and some other severe diseases were excluded. A total of 573 Chinese were prospectively enrolled in this study.

**Primary and secondary outcome measures:** EPVS in basal ganglia (BG) and white matter (WM) were identified on MRI and classified into three categories by the severity. WMH were scored by Fazekas scale. Spearman correlation analysis and ordinal logistic regression analysis were used to determine the relationship between ABP levels and EPVS.

**Results:** There were statistical differences in all of the following ABPV metrics: standard deviation (SD) and coefficient of variation (CV) of systolic blood pressure (SBP), CV of diastolic blood pressure (DBP) in 24-hour, daytime and nighttime and SD of DBP in nighttime among the subgroups stratified by the severity of EPVS in BG. The above ABPV metrics were positively associated with the degree of EPVS in BG. The association between ABPV and EPVS in BG was unchanged after controlling for confounders. Spearman correlation analysis showed ABPV weren't related to the degree of EPVS in WM.

**Conclusion:** ABPV was independently associated with EPVS in BG after controlling for the blood pressure, but not in WM. Pathogenesis of EPVS in BG and WM might be different.

**Keywords** cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

**Strengths and limitations of this study**

- Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments.
- Detailed information on some confounders crucial to the interpretation of EPVS was collected and ordinal logistic regression analysis was performed to determine the independency of association.
- The study was based on hospital physical examinations people in a single center and the cohort may not represent the general population.
- This was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established.

**INTRODUCTION**

Perivascular spaces, or Virchow-Robin spaces, are perivascular compartments surrounding the small penetrating cerebral vessels, serving as an important drainage system for interstitial fluid and solute in brain<sup>1</sup>. They can dilate with accumulation of the interstitial fluid<sup>2, 3</sup>. Enlarged perivascular spaces (EPVS) appear as punctate or linear signal intensities similar to cerebrospinal fluid (CSF) on all MRI sequences in white matter (WM), basal ganglia (BG), hippocampus and brainstem<sup>4, 5</sup>. Recent studies indicated that EPVS were a magnetic resonance imaging (MRI) marker of cerebral small vessel diseases (CSVD) and were associated with other morphological features of CSVD such as white matter hyperintensities (WMH) and lacunes<sup>6, 7</sup>. Some studies found EPVS were associated with impaired cognitive function<sup>5</sup>, incident dementia<sup>8</sup> and sleep disorders<sup>9</sup>. Therefore, it is of clinical importance to understand the risk factors of EPVS and search for treatable methods.

24-hour ambulatory blood pressure monitoring (ABPM) is proven to be a more useful and scientific method to predict blood pressure-related brain damage than single office blood pressure measurements<sup>10, 11</sup>. Ambulatory blood pressure variability

(ABPV) could be well documented by 24-hour ABPM. Previous studies demonstrated higher ABPV increased the risk of cardiovascular events<sup>12, 13</sup>, WMH, lacunar infarction, and cognitive decline<sup>14, 15</sup>. WMH, lacunar infarction and EPVS are all neuroimaging features of CSVD and share some risk factors, such as age and hypertension<sup>16</sup>. However, the relationship between ABPV and EPVS has never been investigated. So in the study, we aimed to investigate whether ABPV was independently associated with EPVS by 24-hour ABPM.

## **METHODS**

### **Study subjects**

We conducted this study as a cross-sectional study. The patients meeting both inclusion and exclusion criteria for physical examinations were prospectively enrolled to avoid selection bias in General Department or Neurology Department of Beijing Chaoyang Hospital Affiliated to Capital Medical University from May 2013 to Jun 2016. They were usual, mandatory and relatively healthy individuals in the Chinese population. The number of arriving patients during the study period, inclusion and exclusion criteria determined the sample size. Inclusion criteria were: (1) patients underwent both brain MRI scans and 24-hour ABPM within 1 month; (2) patients agreed to participate in our study and sign an informed consent. The following patients were excluded: (1) patients with acute stroke, Parkinson disease, dementia, severe traumatic or toxic or infectious brain injury, and brain tumor; (2) patients with severe heart disease, recent myocardial infarction or angina pectoris disorders, severe infections, severe nephrosis or liver disease, thrombotic diseases and tumor; (3) patients with history of severe ischemic (the largest diameter of infarct size > 20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke because of difficulty assessments on EPVS; (4) patients with invalid 24-hour ABPM data (The 24-h ABPM data were considered invalid if measurement was < 70%, < 1 measurement per hour during daytime, and < 6 in total during nighttime).

### **Assessments of EPVS and WMH**

The neurological image examinations were performed in Radiology Department of

our hospital. MR imagines were acquired on a 3.0 T MR scanner (Siemens, Erlangen, Germany).

EPVS were defined as CSF-like signal intensity lesions of round, ovoid, or linear shape of <3mm and located in areas supplied by perforating arteries<sup>6, 17</sup>. We distinguished lacune from EPVS by their larger size (>3mm), spheroid shape and surrounding hyperintensities on FLAIR. WMH were defined as hyperintense signals on T2-weighted and FLAIR and decreased signal intensities on T1-weighted MR imaging.

EPVS in BG and WM were separately assessed according to the scales which were used in other studies<sup>18, 19</sup>. In BG, EPVS were rated according to the number in the slice containing the maximum amount of EPVS. The grades of EPVS were rated as follows: grade 1: < 5 EPVS, grade 2: 5 to 10 EPVS, grade 3: > 10 but still countable, and grade 4: infinite number of EPVS. In WM, EPVS were scored as follows: grade 1: <10 EPVS in total WM, grade 2: >10 in total WM and <10 in the slice containing the maximum number of EPVS, grade 3: 10 to 20 EPVS in the slice containing the maximum number of EPVS, grade 4: > 20 in the slice containing the maximum number of EPVS. We classified EPVS into three categories: degree 1 = grade 1; degree 2 = grade 2; degree 3 = grade 3 or 4.

WMH were scored by Fazekas scale. The detailed description of assessment has been previously published<sup>20</sup>. Periventricular and deep WMH were evaluated separately and totaled together as Fazekas scores.

The intrarater agreement for the rating of EPVS and WMH was assessed on a random sample of 100 individuals with a month interval between the first and second readings. Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information to avoid bias. Random scans of 100 individuals were independently examined by the two experienced neurologists blinded to each other's readings. The *k* statistics of intrarater and interrater agreement was 0.80 or above, indicating good reliability. Disagreement was resolved by discussing with other co-authors.

**24-hour ambulatory blood pressure monitoring**

24-hour ABPM was performed using an automated system (FB-250; Fukuda Denshi, Tokyo, Japan). BP was measured every 30 minutes during the daytime (8:00 AM to 11:00 PM) and every 60 minutes during the nighttime (11:00 PM to 8:00 AM). We excluded a 2-hour transition period around the reported rising and retiring times. The mean systolic blood pressure (SBP), diastolic blood pressure (DBP), coefficient of variation (CV) and standard deviation (SD) of SBP and DBP during 24-hour, daytime, and nighttime were collected. The CV value was defined as the ratio between the SD and the mean SBP or DBP at the same periods. SD and CV were considered as metrics of BPV in this study. Patients continued their previous medication, and we registered the use of anti-hypertension drugs.

### Statistical analysis

Continuous variables were presented as mean values  $\pm$  SD and compared with ANOVA for factors with a normal distribution, whereas no normally distributed variables were compared with Kruskal–Wallis test as appropriate. Categorical variables were expressed as percentages and compared using the chi-square test. Spearman correlation analysis was used to calculate the association between ABPV and the severity of EPVS. In addition, ordinal logistic regression analysis was performed to determine whether the ABPV were independently associated with EPVS after adjustment for other confounders. The results were based on valid data; missing data were excluded. Analyses were performed with Statistical Package for Social Sciences (SPSS version 21.0), and statistical significance was accepted at the  $p < 0.05$ .

## RESULTS

### Baseline characteristics of the study participants

742 patients underwent both brain MRI scans and 24-hour ABPM within 1 month in Medical Care Department or Neurology Department of our hospital from May 2013 to Jun 2016. 40 patients were excluded because of acute stroke, 21 were excluded because of history of severe or hemorrhagic stroke, 15 were excluded because of a history of tumor and 93 were excluded because of invalid ABPM data, leaving 573 patients for the present study. None of them had missing data. There were no



1 statistical differences ( $P>0.05$ ) in age, body mass index, proportion of male, current  
2 smoking, current alcohol, diabetes, hypertension, coronary artery atherosclerosis  
3 disease and using of anti-hypertensive drugs between the excluded subjects and the  
4 final group (Supplementary file). Table 1 showed the characteristics of all enrolled  
5 subjects and subgroups stratified by the degree of EPVS in different brain regions.  
6 Age, Fazekas scale, proportion of hypertension and stroke/TIA, levels of blood urea  
7 nitrogen and creatinine increased with the degree of EPVS in BG increasing. There  
8 were statistical differences in age, Fazekas scale and proportion of coronary artery  
9 atherosclerosis disease (CAD) among subgroups based on the degree of EPVS in  
10 WM.  
11 There were statistical differences in the mean SBP of 24-hour, daytime, and nighttime  
12 among the categories stratified by the degree of EPVS in BG. The results of spearman  
13 correlation analysis showed SBP was positively related to higher degree of EPVS in  
14 BG during all periods (SBP of 24-hour:  $r=0.23$ ,  $p < 0.01$ ; SBP of daytime:  $r=0.25$ ,  $p <$   
15  $0.01$ ; SBP of nighttime:  $r=0.30$ ,  $p < 0.01$ ). The mean DBP of daytime and nighttime  
16 increased with the degree of EPVS in WMH increasing. However, the results of  
17 spearman correlation analysis showed that DBP levels were not associated with higher  
18 numbers of EPVS in CSO ( $p > 0.05$ ).

19 **Table 1.** General characteristics of all enrolled subjects and subgroups stratified by  
20 the severity of EPVS

Characteristics	All patients	EPVS in BG			EPVS in WM		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3
n (%)	573	244 (42.6%)	179 (31.2%)	150 (26.2%)	200 (34.9%)	207 (36.1%)	166 (29.0%)
Age, years	67.8±14.8	61.4±14.4**	67.6±13.8**	78.3±9.6**	70.45±15.2**	66.25±14.4**	66.46±14.3**
Sex, male (%)	355 (62.0)	143 (58.6)	108 (60.3)	104 (69.3)	115 (57.5)	128 (61.8)	112 (67.5)
Current smoking (%)	162 (28.3)	83 (34.0)*	61(34.1)*	18(12.0)*	52 (26.0)	60 (29.0)	50 (30.1)
Current alcohol (%)	126 (22.0)	62 (25.4)*	45 (25.1)*	19 (12.7)*	36 (18.0)	50 (24.2)	40 (24.1)
Hypertension (%)	420 (73.3)	170 (69.7)*	122 (68.2)*	128 (85.3)*	150 (75.0)	145 (70.5)	125 (74.7)
Diabetes (%)	191 (33.3)	78 (32.0)	59 (33.0)	54 (36.0)	71 (35.5)	62 (30.0)	58 (34.9)

CAD (%)	140 (24.4)	48 (19.7)	48 (26.8)	44 (29.3)	61 (30.5) *	45 (21.7) *	34 (20.5) *
Stroke or TIA (%)	125 (21.8)	40 (16.4)**	33 (18.4)**	52 (34.7)**	49 (24.5)	39 (18.8)	37 (22.2)
BMI, kg/m <sup>2</sup>	25.6±3.5	25.6±3.4	25.3±3.5	25.8±3.5	25.8±3.4	25.4±3.5	25.5±3.5
HDL, mmol/L	1.2±0.4	1.2±0.4	1.2±0.4	1.2±0.3	1.2±0.4	1.2±0.4	1.2±0.3
LDL, mmol/L	2.5±0.8	2.5±0.8	2.5±0.8	2.3±0.8	2.4±0.8	2.4±0.8	2.5±0.7
HbA1c, %	6.4±1.3	6.4±1.3	6.4±1.4	6.5±1.2	6.4±1.1	6.5±1.4	6.5±1.4
BUN, mmol/L	5.8±2.1	5.5±1.7**	5.9±2.6**	6.3±2.0**	6.0±2.5	5.7±1.9	5.8±1.9
Creatinine, umol/L	79.1±27.1	74.0±19.3**	81.7±32.6**	84.2±29.4**	81.2±27.4	77.7±27.3	78.3±26.4
Fazekas scale	3.1±1.8	2.2±1.4**	3.1±1.7**	4.7±1.5**	3.5±2.0**	2.9±1.7**	3.1±1.7**
Using of anti-hypertensive drugs (%)	342 (59.7)	130 (53.3) *	96 (53.6) *	116 (77.3) *	129 (64.5)	114 (55.1)	99 (59.6)
Class of anti-hypertensive drugs							
Dihydropyridinic CCB (%)	226 (39.4)	74 (30.3)	67 (37.4)	63 (42.0)	69 (34.5)	79 (38.2)	55 (33.1)
ACEI (%)	26 (4.5)	11 (4.5)	6 (3.4)	9 (6.0)	8 (4.0)	9 (4.3)	9 (5.7)
ARB (%)	160 (27.9)	70 (28.7)	46 (25.7)	44 (29.3)	69 (34.5) *	52 (25.1) *	39 (23.5) *
β-Blockers (%)	96 (16.8)	34 (13.9)	28 (15.6)	34 (22.7)	40 (20.0)	31 (15.0)	25 (15.1)
Nonloop diuretics (%)	39 (6.8)	20 (8.2)	12 (6.7)	7 (4.7)	16 (8.0)	13 (6.3)	10 (6.0)
24-hour							
SBP (mmHg)	133±16.4	129±15.6**	134±16.0**	138±16.5**	133±16.5	132±17.1	132.9±15.4
DBP (mmHg)	76±9.6	77±9.5	76±10.0	75±9.1	75±9.5*	76±9.6*	77±9.6*
Daytime							
SBP (mmHg)	135±16.6	130±16.0**	135±16.0**	141±16.4**	135±16.6	134±17.6	135±15.3
DBP (mmHg)	77±10.0	77±10.0*	77±10.3*	75±9.5*	75±9.9*	77±10.1*	78±9.9*
Nighttime							
SBP (mmHg)	129±19.8	123±18.5**	131±18.9**	137±19.9**	130±20.8	128±19.5	129±19.0
DBP (mmHg)	74±10.7	74±10.5	73±11.2	74±10.4	723±10.8	74±10.5	75±10.8

- 1 EPVS, enlarged perivascular spaces; BG, basal ganglia; WM, white matter; BMI,
- 2 body mass index; CAD, coronary artery atherosclerosis disease; TIA, transient
- 3 ischemic attack; HDL, high-density lipoprotein; LDL, low-density lipoprotein;
- 4 HbA1c, hemoglobin A1c; BUN, blood urea nitrogen, CCB, calcium-channel blocker;

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. \*  $p < 0.05$ , \*\*  $p < 0.01$ .

**Association between ABPV and EPVS in BG**

SD and CV of ambulatory blood pressure in different categories stratified by the degree of EPVS in BG were presented in Table 2. There were statistical differences ( $p < 0.05$ ) in all of the following BPV metrics: SD and CV of SBP, CV of DBP during 24-hour, daytime and nighttime and SD of DBP during nighttime among the three subgroups stratified by the severity of EPVS in BG. These metrics gradually increased with the degree of EPVS increasing (Fig 1-3). The results of spearman correlation analysis demonstrated these metrics were positively associated with the degree of EPVS in BG ( $r > 0$ ,  $P < 0.05$ ) (Table 3). The association between ABPV and EPVS were unchanged after controlling for demographic confounders (model 1), Fazekas scale (model 2) and the mean SBP or DBP during the same period (model 3), which indicated that the ABPV were independently associated with EPVS in BG. The results of ordinal logistic regression analysis were presented in Table 4.

**Association between ABP Levels and EPVS in WM**

SD and CV of ambulatory blood pressure in different categories stratified by degree of EPVS in WM were also presented in Table 2. There were statistical differences ( $p < 0.05$ ) in SD of SBP, CV of SBP, SD of DBP and CV of DBP during 24-hour and daytime among the three categories. However, there were not linear trend among the three subgroups. The results of spearman correlation analysis showed there were no linear correlation between these metrics and the degree of EPVS in WM (Table 3).

**Table 2.** Results of ABPV in all subjects and subgroups stratified by the severity of EPVS

	All patients	EPVS in BG				EPVS in WM			
		Degree 1	Degree 2	Degree 3	P	Degree 1	Degree 2	Degree 3	P
24-hour									
SD of SBP, mmHg	18.28±5.27	16.93±4.76	18.57±4.56	20.13±6.21	<0.001	18.86±5.56	17.36±5.11	18.73±4.99	0.004

SD of DBP, mmHg	12.56±3.58	12.22±3.56	12.62±3.34	13.05±3.86	0.149	12.83±3.76	11.85±3.32	13.14±3.56	0.001
CV of SBP, %	13.83±3.80	13.21±3.56	13.99±3.54	14.64±4.26	0.004	14.16±3.87	13.23±3.70	14.18±3.76	0.028
CV of DBP, %	16.68±4.74	16.03±4.68	16.82±4.46	17.55±5.04	0.013	17.22±4.76	15.78±4.72	17.14±4.60	0.001
Daytime									
SD of SBP, mmHg	18.02±5.70	16.66±4.93	18.21±5.35	19.99±6.65	<0.001	18.68±5.98	16.99±5.47	18.50±5.49	0.004
SD of DBP, mmHg	12.56±4.01	12.25±3.80	12.51±3.93	13.12±4.40	0.241	12.81±4.06	11.76±3.71	13.26±4.17	0.001
CV of SBP, %	13.45±4.08	12.84±3.75	13.62±4.14	14.26±4.38	0.005	13.86±4.16	12.76±3.88	13.81±4.12	0.016
CV of DBP, %	16.48±5.19	15.84±4.77	16.47±5.24	17.54±5.63	0.024	16.98±4.88	15.47±5.12	17.15±5.48	0.002
Nighttime									
SD of SBP, mmHg	15.21±7.37	13.79±7.71	15.18±5.74	17.54±7.97	<0.001	15.08±6.09	14.94±8.66	15.69±7.05	0.180
SD of DBP, mmHg	10.43±4.50	9.81±4.33	10.77±4.55	11.03±4.61	0.010	10.23±4.11	10.26±4.58	10.88±4.84	0.247
CV of SBP, %	11.85±5.37	11.22±5.53	11.77±4.56	12.95±5.84	0.005	11.69±4.62	11.70±5.95	12.23±5.48	0.411
CV of DBP, %	14.26±6.02	13.42±5.88	14.75±5.89	15.03±6.28	0.003	14.20±5.61	14.08±6.30	14.54±6.17	0.426

1 SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of  
 2 variation; SD: standard deviation.

3 **Table 3.** Results of spearman correlation analysis between the degree of EPVS and  
 4 ABPV

	EPVS in BG		EPVS in WM	
	r	P value	r	P value
24h				
SD of SBP	0.216	0.000	-0.013	0.762
SD of DBP	0.082	0.051	0.030	0.481
CV of SBP	0.137	0.001	-0.008	0.854
CV of DBP	0.123	0.003	-0.028	0.505
Daytime				

SD of SBP	0.205	0.000	-0.024	0.562
SD of DBP	0.065	0.120	0.031	0.459
CV of SBP	0.135	0.001	-0.023	0.585
CV of DBP	0.109	0.009	-0.017	0.679
Nighttime				
SD of SBP	0.229	0.000	0.020	0.637
SD of DBP	0.125	0.003	0.043	0.309
CV of SBP	0.136	0.001	0.027	0.521
CV of DBP	0.135	0.001	0.007	0.870

SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of variation; SD: standard deviation.

**Table 4.** Results of ordinal logistic regression analysis between ABPV and EPVS in BG

	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
24h						
SD of SBP	1.55 (1.32-1.83)	<0.001	1.48 (1.25-1.75)	<0.001	1.41 (1.19-1.68)	<0.001
CV of SBP	1.47 (1.19-1.83)	<0.001	1.48 (1.18-1.85)	0.001	1.60 (1.27-2.02)	<0.001
CV of DBP	1.59 (1.13-2.24)	0.008	1.69 (1.18-2.42)	0.004	1.81 (1.25-2.60)	0.001
Daytime						
SD of SBP	1.44 (1.25-1.67)	<0.001	1.39 (1.19-1.61)	<0.001	1.31 (1.12-1.54)	0.001
CV of SBP	1.32 (1.08-1.61)	0.006	1.32 (1.08-1.62)	0.008	1.43 (1.16-1.77)	0.001
CV of DBP	1.49 (1.10-2.04)	0.011	1.59 (1.15-2.19)	0.005	1.67 (1.21-2.31)	0.002
Nighttime						
SD of SBP	1.29 (1.15-1.46)	<0.001	1.25 (1.11-1.40)	<0.001	1.21 (1.07-1.37)	0.002
SD of DBP	1.39 (1.15-1.67)	<0.001	1.33 (1.11-1.61)	0.003	1.31 (1.12-1.54)	0.001
CV of SBP	1.27 (1.09-1.48)	0.002	1.26 (1.08-1.47)	0.003	1.31 (1.08-1.58)	0.006
CV of DBP	1.19 (1.04-1.36)	0.013	1.20 (1.04-1.37)	0.012	1.21 (1.05-1.39)	0.008

Results of ordinal regression analysis presented as OR per 5% increase in CV of

1 blood pressure and 5 mmHg in SD of blood pressure.

2 Model1: adjusted for age, smoking, alcohol, hypertension, stroke/TIA, BUN,  
3 creatinine and using of anti-hypertensive drugs.

4 Model2: model 1 + Fazekas scale.

5 Model3: model 2 + the mean SBP or DBP during the same period.

## 6 **DISCUSSION**

7 In this study, we explored the relationship between ABPV and EPVS based on  
8 hospital physical examinations population. Our data suggested that all of the  
9 following metrics: SD of SBP, CV of SBP and CV of DBP during 24-hour, daytime  
10 and nighttime and SD of DBP during nighttime were positively associated with the  
11 degree of EPVS in BG. The association between the above ABPV metrics and EPVS  
12 in BG were unchanged after controlling for demographic confounders, Fazekas scale  
13 and the mean SBP or DBP during the same period. Although there were statistical  
14 differences ABPV metrics in 24-hour and daytime among the three subgroups  
15 stratified by EPVS severity in WM, there were not linear correlation between ABPV  
16 and the degree of EPVS in WM. In addition, we found age, Fazekas scale,  
17 hypertension, stroke/transient ischemic attack (TIA), levels of blood urea nitrogen and  
18 creatinine were positively associated with the degree of EPVS in BG.

19 There were methodological strengths of our study. We recruited participants strictly  
20 according to inclusion and exclusion criteria to avoid selection bias. The patients with  
21 acute cerebrovascular and cardiovascular disorders were excluded to avoid the impact  
22 of the acute stroke, recent myocardial infarction or angina pectoris on blood pressure.  
23 The patients with history of severe ischemic (the largest diameter of infarct size >  
24 20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or  
25 hemorrhagic stroke were exclude because of difficulty and inaccurate assessments on  
26 EPVS. In addition, assessments of EPVS and WMH were performed by two  
27 experienced neurologists blinded to clinical information and disagreements were  
28 resolved by consensus, which ensure the accuracy of the assessments. We collected  
29 detailed information on vascular confounders, WMH, levels of blood urea nitrogen  
30 and creatinine, which are crucial to the interpretation of EPVS<sup>6, 21</sup>. So we think the

1 reliability of the data is high. There were some limitations in our study. First, our  
2 study was based on hospital physical examinations people in a single center and the  
3 cohort may not represent the general population. According to our observation, these  
4 people had a higher material standard of living than the general population in China,  
5 and some of them showed more anxiety symptoms. But it's regrettable that we didn't  
6 assess the anxiety symptoms by the Hamilton Anxiety Rating Scale and didn't collect  
7 the patients' education level. Second, this was a cross-sectional study, and the causal  
8 relationship between ABPV and EPVS could not be established. Third, all participants  
9 underwent 24-hour ABPM which could only show short-term ABPV. It has been  
10 demonstrated that the prognostic significance of BPV on vascular diseases is weaker  
11 for short-term than for long-term BPV<sup>22</sup>.  
12 This is the first study to investigate the relationship between ABPV and EPVS.  
13 Previously, several studies investigated the relationship between EPVS and  
14 hypertension. In a prospective, multicenter, hospital-based study, Zhang CQ et al<sup>19</sup>  
15 found hypertension was associated with the severity of EPVS in WM, not in BG.  
16 Klarenbeek P et al<sup>23</sup> investigated the association between ABP levels and EPVS in  
17 first-ever lacunar stroke patients. They found higher day systolic, day diastolic and  
18 24-hour diastolic BP levels were independently associated EPVS in BG, and no  
19 relation between ABP levels and EPVS in WM. We also analyzed the correlation  
20 between ABP levels and EPVS. We found ABP levels were associated with EPVS in  
21 BG, but not in WMH, which is in agreement with Klarenbeek P et al.'s study.  
22 However, we found only SBP was positively related to higher degree of EPVS in BG  
23 in all periods, and no relation between DBP and EPVS, which are different from  
24 previous results. The different study population and different scoring methods of  
25 assessing EPVS may partly lead to the different results. Our data suggested that SD of  
26 SBP, CV of SBP and CV of DBP in all periods were positively associated with the  
27 degree of EPVS in BG, but not in WM. The present study couldn't explain the  
28 phenomenon. This may be caused by different pathogenesis of EPVS at the different  
29 locations<sup>18, 19, 24</sup>. Previous studies have found the anatomical structure of EPVS  
30 located in BG and WM were different<sup>25</sup>. The arteries in the basal ganglia are



surrounded by 2 distinct coats of leptomeninges separated by a perivascular space which is continuous with the perivascular space around arteries in the subarachnoid space. Whereas there are only single periarterial layer of leptomeninges surrounding the arteries in the cerebral cortex and they penetrate into the white matter. Drainage of interstitial fluid from the brain to cervical lymph nodes may be mainly along perivascular spaces in WM rather than in BG<sup>3, 26</sup>. In addition, the effect of age, hypertension on EPVS seems to be stronger for EPVS located in BG than for those located in WM<sup>18</sup>. Similarly, the association between EPVS and the load of WMH, taken as a marker of CSVD, also appears to be stronger in BG than in WM. Thus, their dilation may present differences in terms of risk factors as well as in mechanisms in BG and WM. However, the reason why SBP related differently in these two locations remains unclear because there are a very limited number of studies on mechanisms underlying dilation of perivascular spaces in BG and WM. Several studies have demonstrated higher ABPV increased the risk of neuroimaging features of CSVD, such as WMH and lacunar infarction<sup>14, 15</sup>. Our results found higher ABPV was independently with higher degree of EPVS in BG, which support the notion that EPVS in BG are a separate marker of CSVD.

An increased permeability of the small vessel walls and blood brain barrier (BBB) are considered to contribute to the development of EPVS, which has been reported to be associated with damage of microvascular endothelial cells and their tight junctions<sup>1, 16, 27</sup>. Higher ABPV would lead to more mechanical stress on the wall vessel, endothelial injury<sup>28</sup> and arterial stiffness<sup>29</sup>. So, it is reasonable that high ABPV contribute to the development of EPVS by the damage to endothelial cell. Our results may remind clinicians that they should pay attention to patients' ABPV and lower patients' ABPV in their clinical work. In the future, the causal relationship between ABPV and EPVS should be established in a prospective cohort study. And the relationship between ABPV and EPVS should be explored.

## CONCLUSION

SD of SBP, CV of SBP and CV of DBP during all periods and SD of DBP during nighttime were positively associated with the degree of EPVS in BG. The association



was unchanged after controlling for confounders. No relation was found between ABPV and EPVS in WM. It is important for clinicians to reduce both patients' high blood pressure levels and ABPV.

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**Conflict of Interest** None declared.

**Ethic approval** The study was approved by the Ethics Committee of Beijing Chaoyang Hospital Affiliated to Capital Medical University and was performed in accordance with the declaration of Helsinki.

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**Figure 1.** The ABPV metrics of subgroups stratified by EPVS severity in BG during 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

**Figure 2.** The ABPV metrics of subgroups stratified by EPVS severity in BG during daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

**Figure 3.** The ABPV metrics of subgroups stratified by EPVS severity in BG during nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

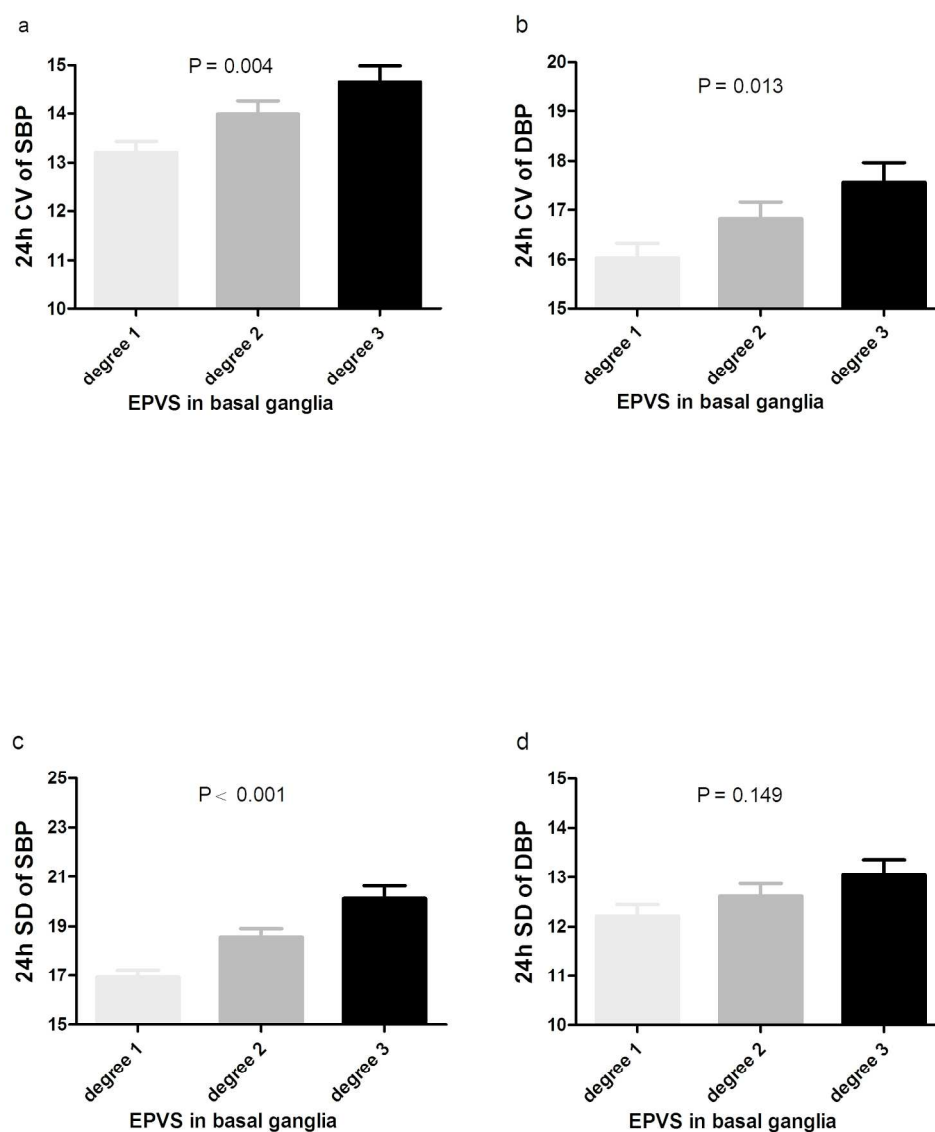


Figure 1. The ABPV metrics of subgroups stratified by EPVS severity in BG during 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

191x228mm (300 x 300 DPI)

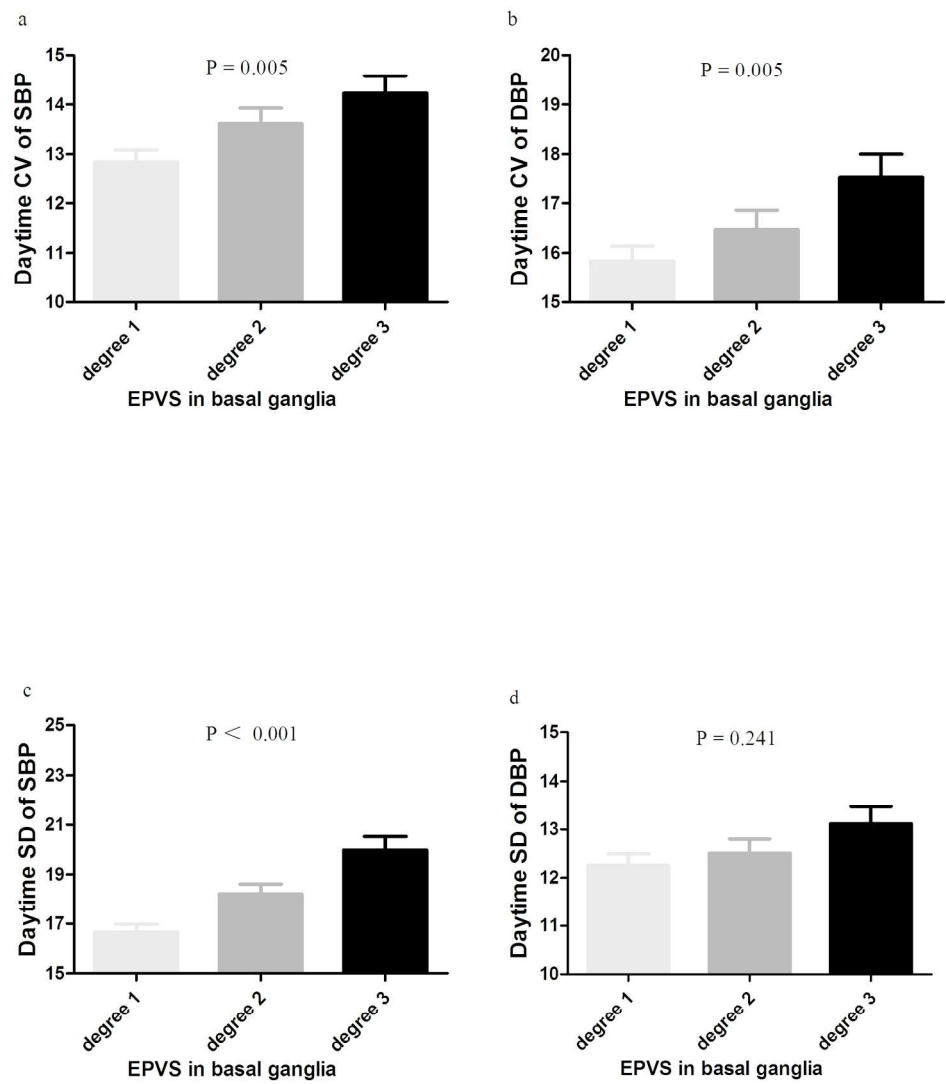


Figure 2. The ABPV metrics of subgroups stratified by EPVS severity in BG during daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

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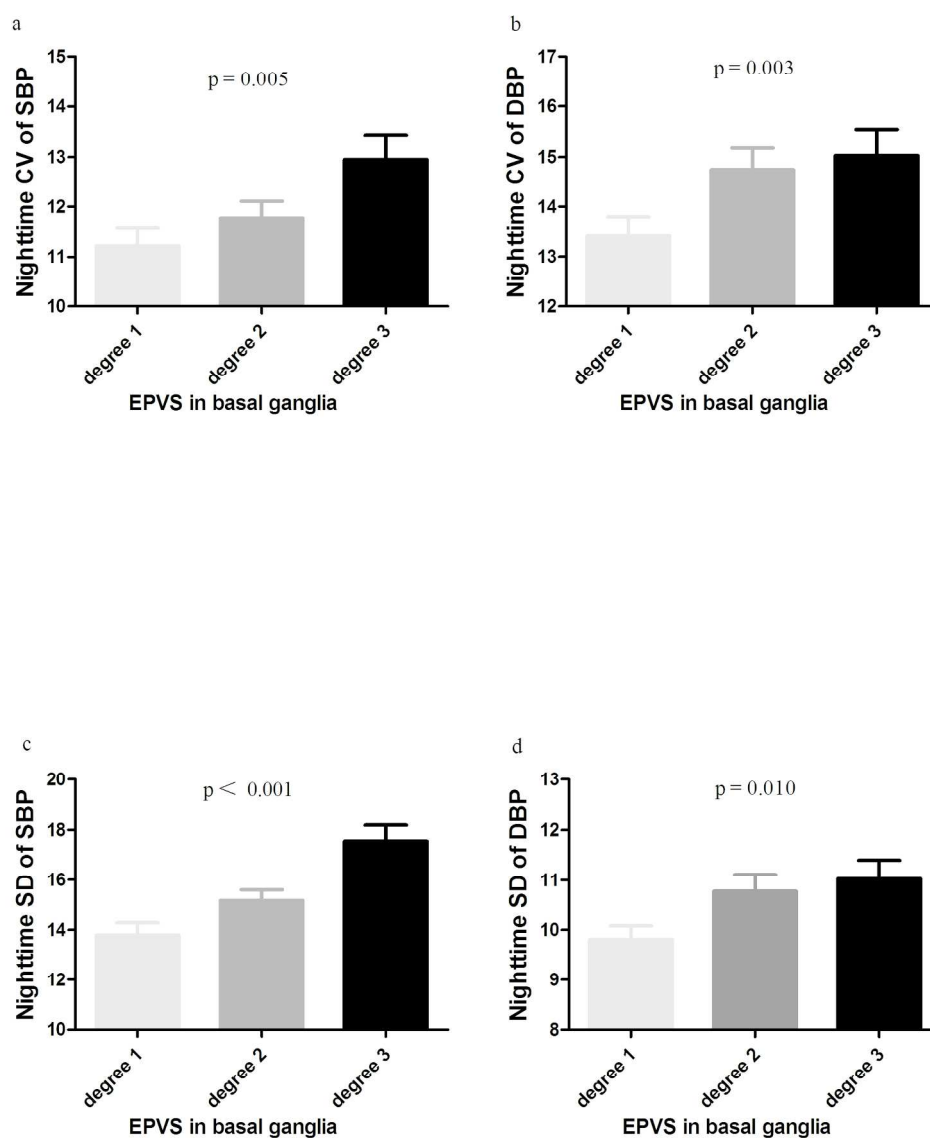
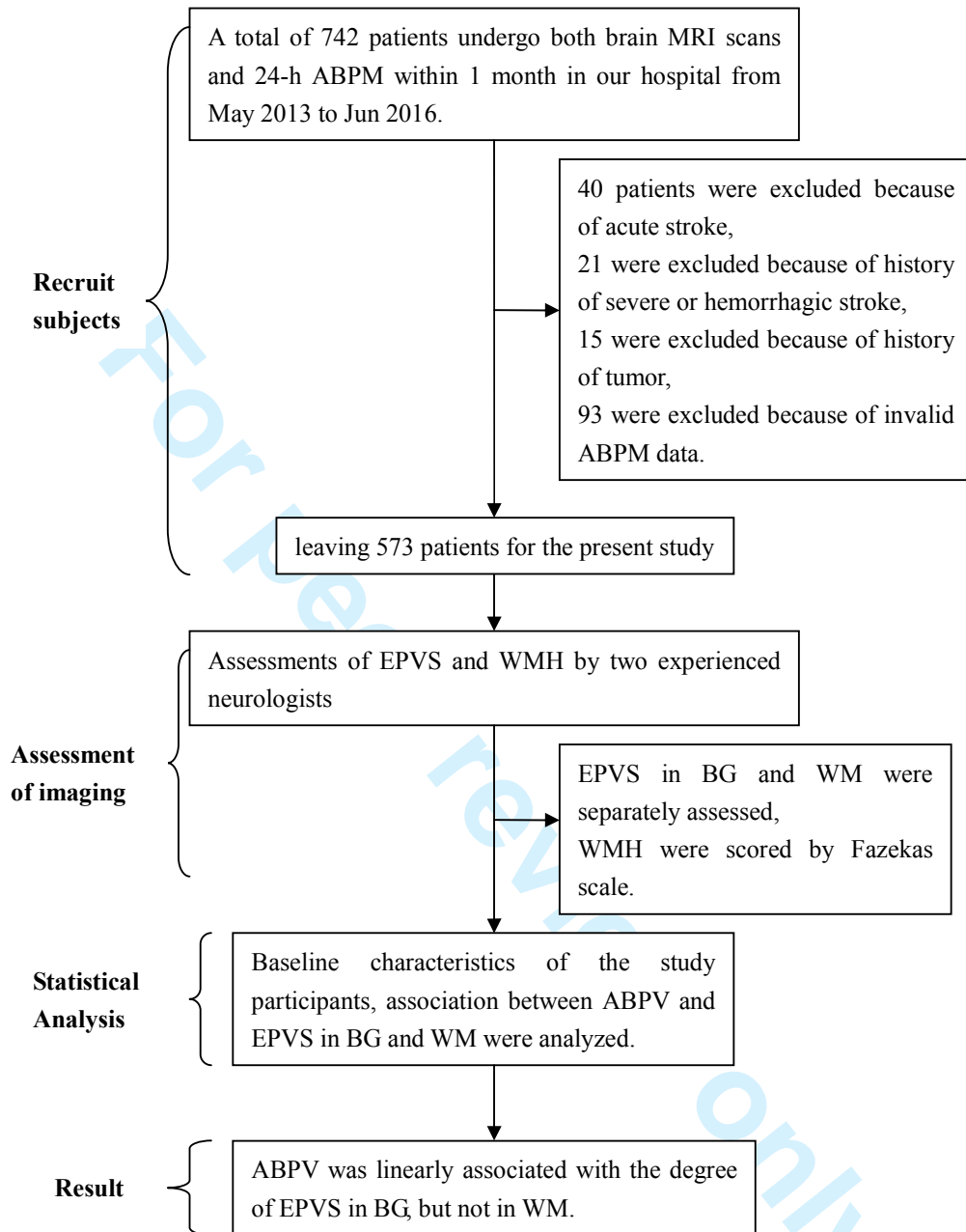


Figure 3. The ABPV metrics of subgroups stratified by EPVS severity in BG during nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

189x227mm (300 x 300 DPI)

The comparison of general clinical characteristics between the included and excluded participants

Characteristics	enrolled patients	excluded patients	P
n	573	169	-
Age, years	67.8±14.8	69.6±9.6	0.443
Sex, male (%)	355 (62.0)	101(59.8)	0.607
Current smoking (%)	162 (28.3)	55(32.5)	0.283
Current alcohol (%)	126 (22.0)	42(24.9)	0.435
Hypertension (%)	420 (73.3)	115(68.0)	0.181
Diabetes (%)	191 (33.3)	44(26.0)	0.073
coronary atherosclerosis disease (%)	140 (24.4)	35(20.7)	0.316
body mass index, kg/m <sup>2</sup>	25.6±3.5	25.1±3.0	0.160
Using of anti-hypertensive drugs (%)	342 (59.7)	99(58.6)	0.797



ABPM, ambulatory blood pressure monitoring; EPVS, enlarged perivascular spaces; WMH, white matter hyperintensities; BG, basal ganglia; WM, white matter.



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	P1 and 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	P2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	P4
Methods			
Study design	4	Present key elements of study design early in the paper	P4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	P4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P5-6
Bias	9	Describe any efforts to address potential sources of bias	P4 and 5

Study size	10	Explain how the study size was arrived at	P4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	P6
		(b) Describe any methods used to examine subgroups and interactions	P6
		(c) Explain how missing data were addressed	P6
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P6
		(b) Give reasons for non-participation at each stage	P6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P7
		(b) Indicate number of participants with missing data for each variable of interest	P7
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P6-12
		(b) Report category boundaries when continuous variables were categorized	

		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	P12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	P14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P15

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

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**1     The relationship between ambulatory blood pressure variability and**  
**2     enlarged perivascular spaces: a cross-sectional study**

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## Abstract

**Objectives:** Recent studies reported that 24-hour ambulatory blood pressure variability (ABPV) was associated with lacunar infarction and white matter hyperintensities (WMH). However, the relationship between ABPV and enlarged perivascular spaces (EPVS) hasn't been investigated. Thus, our study aimed to investigate whether ABPV is associated with EPVS by 24-hour ambulatory blood pressure monitoring (ABPM).

**Design:** We conducted this study as a cross-sectional study.

**Settings:** The study was based on patients who presented for physical examinations in our hospital from May 2013 to Jun 2016.

**Participants:** Patients with both brain MRI scans and 24-hour ABPM were included and patients with acute stroke, a history of severe stroke and some other severe diseases were excluded. A total of 573 Chinese patients were prospectively enrolled in this study.

**Primary and secondary outcome measures:** EPVS in basal ganglia (BG) and white matter (WM) were identified on MRI and classified into three categories by the severity. WMH were scored by Fazekas scale. Coefficient of variation (CV) and standard deviation (SD) were considered as metrics of ABPV. Spearman correlation analysis and ordinal logistic regression analysis were used to assess the relationship between ABPV and EPVS.

**Results:** There were statistical differences among the subgroups stratified by the severity of EPVS in BG in the following ABPV metrics: SD and CV of systolic blood pressure (SBP), CV of diastolic blood pressure (DBP) in 24-hour, daytime and nighttime and SD of DBP in nighttime. The above ABPV metrics were positively associated with the degree of EPVS. The association was unchanged after adjusting for confounders. Spearman correlation analysis showed ABPV wasn't related to the degree of EPVS in WM.

**Conclusion:** ABPV was independently associated with EPVS in BG after controlling for the blood pressure, but not in WM. Pathogenesis of EPVS in BG and WM might be different.

**Keywords** cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

**Strengths and limitations of this study**

- Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments.
- Detailed information on some confounders crucial to the interpretation of EPVS was collected and ordinal logistic regression analysis was performed to determine the independency of association.
- The study was based on a population who presented to the hospital for physical exam in a single center and the cohort may not represent the general population.
- This was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established.

**INTRODUCTION**

Perivascular spaces, or Virchow-Robin spaces, are perivascular compartments surrounding the small penetrating cerebral vessels, serving as an important drainage system for interstitial fluids and solute in the brain<sup>1</sup>. They can dilate with accumulation of the interstitial fluids<sup>2, 3</sup>. Enlarged perivascular spaces (EPVS) appear as punctate or linear signal intensities similar to cerebrospinal fluids (CSF) on all MRI sequences in white matter (WM), basal ganglia (BG), hippocampus and brainstem<sup>4, 5</sup>. Recent studies indicated that EPVS were a magnetic resonance imaging (MRI) marker of cerebral small vessel diseases (CSVD) and were associated with other morphological features of CSVD such as white matter hyperintensities (WMH) and lacunes<sup>6, 7</sup>. Some studies found EPVS were associated with impaired cognitive function<sup>5</sup>, incident dementia<sup>8</sup> and sleep disorders<sup>9</sup>. Therefore, it is of clinical importance to understand the risk factors for EPVS and search for treatable options in the future.

24-hour ambulatory blood pressure monitoring (ABPM) is proven to be a more useful and scientific method to predict blood pressure-related brain damage than single

office blood pressure measurement<sup>10, 11</sup>. Ambulatory blood pressure variability (ABPV) could be well documented by 24-hour ABPM. Previous studies demonstrated higher ABPV increased the risk of cardiovascular events<sup>12, 13</sup>, WMH, lacunar infarction, and cognitive decline<sup>14, 15</sup>. WMH, lacunar infarction and EPVS are all neuroimaging features of CSVD and share some risk factors, such as age and hypertension<sup>16</sup>. However, the relationship between ABPV and EPVS has never been investigated. Thus in the present study, we aimed to investigate whether ABPV, which was reflected by 24-hour ABPM, was independently associated with EPVS.

## METHODS

### Study subjects

We conducted this study as a cross-sectional study. The patients who presented for physical examination to Medicine Department or Neurology Department of Beijing Chaoyang Hospital Affiliated to Capital Medical University were prospectively identified from May 2013 to Jun 2016. They were screened according to our inclusion and exclusion criteria. The number of arriving patients during the study period, inclusion and exclusion criteria determined the sample size. Inclusion criteria were: (1) patients underwent both brain MRI scans and 24-hour ABPM within 1 month; (2) patients agreed to participate in our study and signed an informed consent. The following patients were excluded: (1) patients with acute stroke, Parkinson disease, dementia, severe traumatic or toxic or infectious brain injury, and brain tumor; (2) patients with severe heart disease, recent myocardial infarction or angina pectoris disorders, severe infections, severe nephrosis or liver disease, thrombotic diseases and tumor; (3) patients with history of severe ischemic (the largest diameter of infarct size >20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke because of difficulty assessments on EPVS; (4) patients with invalid 24-hour ABPM data (The 24-h ABPM data were considered invalid if measurement was < 70%, < 1 measurement per hour during daytime, and < 6 in total during nighttime).

### Assessments of EPVS and WMH

The neurological image examinations were performed in Radiology Department of



our hospital. MR imagines were acquired on a 3.0 T MR scanner (Siemens, Erlangen, Germany).

EPVS were defined as CSF-like signal intensity lesions of round, ovoid, or linear shape of <3mm and located in areas supplied by perforating arteries<sup>6, 17</sup>. We distinguished lacune from EPVS by their larger size (>3mm), spheroid shape and surrounding hyperintensities on FLAIR. WMH were defined as hyperintense signals on T2-weighted and FLAIR and decreased signal intensities on T1-weighted MR imaging.

EPVS in BG and WM were separately assessed according to the scales which were used in other studies<sup>18, 19</sup>. In BG, EPVS were rated according to the number in the slice containing the maximum amount of EPVS. The grades of EPVS were rated as following: grade 1: < 5 EPVS, grade 2: 5 to 10 EPVS, grade 3: > 10 but still countable, and grade 4: infinite number of EPVS. In WM, EPVS were scored as follows: grade 1: <10 EPVS in total WM, grade 2: >10 in total WM and <10 in the slice containing the maximum number of EPVS, grade 3: 10 to 20 EPVS in the slice containing the maximum number of EPVS, grade 4: > 20 in the slice containing the maximum number of EPVS. We classified EPVS into three categories: degree 1 = grade 1; degree 2 = grade 2; degree 3 = grade 3 or 4.

WMH were scored by Fazekas scale. The detailed description of assessments has been previously published<sup>20</sup>. Periventricular and deep WMH were evaluated separately and then added together as Fazekas scores.

The intrarater agreement for the rating of EPVS and WMH was assessed on a random sample of 100 individuals with a month interval between the first and second readings. Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information to avoid bias. Random scans of 100 individuals were independently examined by the two experienced neurologists blinded to each other's readings. The *k* statistics of intrarater and interrater agreement was 0.80 or above, indicating good reliability. Disagreement was resolved by discussing with other co-authors.

**24-hour ambulatory blood pressure monitoring**

24-hour ABPM was performed using an automated system (FB-250; Fukuda Denshi, Tokyo, Japan). BP was measured every 30 minutes during the daytime (8:00 AM to 11:00 PM) and every 60 minutes during the nighttime (11:00 PM to 8:00 AM). We excluded a 2-hour transition period around the reported rising and retiring times. The mean systolic blood pressure (SBP), diastolic blood pressure (DBP), coefficient of variation (CV) and standard deviation (SD) of SBP and DBP during 24-hour, daytime, and nighttime were collected. The CV value was defined as the ratio between the SD and the mean SBP or DBP at the same periods. SD and CV were considered as metrics of BPV in this study. Patients continued taking their previous medications, and we registered the use of anti-hypertension drugs.

### Statistical analysis

Continuous variables were presented as mean values  $\pm$  SD and compared with ANOVA for factors with a normal distribution, whereas no normally distributed variables were compared with Kruskal–Wallis test as appropriate. Categorical variables were expressed as percentages and compared using the chi-square test. Spearman correlation analysis was used to calculate the association between ABPV and the severity of EPVS. In addition, ordinal logistic regression analysis was performed to determine whether the ABPV was independently associated with EPVS after adjusting for other confounders. The results were based on valid data; missing data were excluded. Analyses were performed with Statistical Package for Social Sciences (SPSS version 21.0), and statistical significance was accepted at the  $p < 0.05$ .

## RESULTS

### Baseline characteristics of the study participants

742 patients underwent both brain MRI scans and 24-hour ABPM within 1 month in the Medicine Department or Neurology Department of our hospital from May 2013 to Jun 2016. 40 patients were excluded because of acute stroke, 21 were excluded because of history of severe or hemorrhagic stroke, 15 were excluded because of a history of tumor and 93 were excluded because of invalid ABPM data, leaving 573 patients enrolled in the present study. None of them had missing data. There were no

1 statistical differences ( $P>0.05$ ) in age, body mass index, proportion of male, current  
2 smoking, current alcohol, diabetes, hypertension, coronary artery atherosclerosis  
3 disease and using of anti-hypertensive drugs between the excluded subjects and the  
4 final group (Supplementary file). Table 1 showed the characteristics of all enrolled  
5 subjects and subgroups stratified by the degree of EPVS in different brain regions.  
6 Age, Fazekas scale, proportion of hypertension and stroke/TIA, levels of blood urea  
7 nitrogen and creatinine increased with the degree of EPVS in BG increasing. There  
8 were statistical differences in age, Fazekas scale and proportion of coronary artery  
9 atherosclerosis disease (CAD) among subgroups based on the degree of EPVS in  
10 WM.  
11 There were statistical differences in the mean SBP during 24-hour, daytime, and  
12 nighttime among the categories stratified by the degree of EPVS in BG. The results of  
13 spearman correlation analysis showed SBP was positively related to higher degree of  
14 EPVS in BG during all periods (SBP of 24-hour:  $r=0.23$ ,  $p < 0.01$ ; SBP of daytime:  
15  $r=0.25$ ,  $p < 0.01$ ; SBP of nighttime:  $r=0.30$ ,  $p < 0.01$ ). The mean DBP of daytime and  
16 nighttime increased with the degree of EPVS in WMH increasing. However, the  
17 results of spearman correlation analysis showed that DBP levels were not associated  
18 with higher numbers of EPVS in CSO ( $p > 0.05$ ).

19 **Table 1.** General characteristics of all enrolled subjects and subgroups stratified by  
20 the severity of EPVS

Characteristics	All patients	EPVS in BG			EPVS in WM		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3
n (%)	573	244 (42.6%)	179 (31.2%)	150 (26.2%)	200 (34.9%)	207 (36.1%)	166 (29.0%)
Age, years	67.8±14.8	61.4±14.4**	67.6±13.8**	78.3±9.6**	70.45±15.2**	66.25±14.4**	66.46±14.3**
Sex, male (%)	355 (62.0)	143 (58.6)	108 (60.3)	104 (69.3)	115 (57.5)	128 (61.8)	112 (67.5)
Current smoking (%)	162 (28.3)	83 (34.0)*	61(34.1)*	18(12.0)*	52 (26.0)	60 (29.0)	50 (30.1)
Current alcohol (%)	126 (22.0)	62 (25.4)*	45 (25.1)*	19 (12.7)*	36 (18.0)	50 (24.2)	40 (24.1)
Hypertension (%)	420 (73.3)	170 (69.7)*	122 (68.2)*	128 (85.3)*	150 (75.0)	145 (70.5)	125 (74.7)
Diabetes (%)	191 (33.3)	78 (32.0)	59 (33.0)	54 (36.0)	71 (35.5)	62 (30.0)	58 (34.9)

CAD (%)	140 (24.4)	48 (19.7)	48 (26.8)	44 (29.3)	61 (30.5) *	45 (21.7) *	34 (20.5) *
Stroke or TIA (%)	125 (21.8)	40 (16.4)**	33 (18.4)**	52 (34.7)**	49 (24.5)	39 (18.8)	37 (22.2)
BMI, kg/m <sup>2</sup>	25.6±3.5	25.6±3.4	25.3±3.5	25.8±3.5	25.8±3.4	25.4±3.5	25.5±3.5
HDL, mmol/L	1.2±0.4	1.2±0.4	1.2±0.4	1.2±0.3	1.2±0.4	1.2±0.4	1.2±0.3
LDL, mmol/L	2.5±0.8	2.5±0.8	2.5±0.8	2.3±0.8	2.4±0.8	2.4±0.8	2.5±0.7
HbA1c, %	6.4±1.3	6.4±1.3	6.4±1.4	6.5±1.2	6.4±1.1	6.5±1.4	6.5±1.4
BUN, mmol/L	5.8±2.1	5.5±1.7**	5.9±2.6**	6.3±2.0**	6.0±2.5	5.7±1.9	5.8±1.9
Creatinine, umol/L	79.1±27.1	74.0±19.3**	81.7±32.6**	84.2±29.4**	81.2±27.4	77.7±27.3	78.3±26.4
Fazekas scale	3.1±1.8	2.2±1.4**	3.1±1.7**	4.7±1.5**	3.5±2.0**	2.9±1.7**	3.1±1.7**
Using of anti-hypertensive drugs (%)	342 (59.7)	130 (53.3) *	96 (53.6) *	116 (77.3) *	129 (64.5)	114 (55.1)	99 (59.6)
Class of anti-hypertensive drugs							
Dihydropyridinic CCB (%)	226 (39.4)	74 (30.3)	67 (37.4)	63 (42.0)	69 (34.5)	79 (38.2)	55 (33.1)
ACEI (%)	26 (4.5)	11 (4.5)	6 (3.4)	9 (6.0)	8 (4.0)	9 (4.3)	9 (5.7)
ARB (%)	160 (27.9)	70 (28.7)	46 (25.7)	44 (29.3)	69 (34.5) *	52 (25.1) *	39 (23.5) *
β-Blockers (%)	96 (16.8)	34 (13.9)	28 (15.6)	34 (22.7)	40 (20.0)	31 (15.0)	25 (15.1)
Nonloop diuretics (%)	39 (6.8)	20 (8.2)	12 (6.7)	7 (4.7)	16 (8.0)	13 (6.3)	10 (6.0)
24-hour							
SBP (mmHg)	133±16.4	129±15.6**	134±16.0**	138±16.5**	133±16.5	132±17.1	132.9±15.4
DBP (mmHg)	76±9.6	77±9.5	76±10.0	75±9.1	75±9.5*	76±9.6*	77±9.6*
Daytime							
SBP (mmHg)	135±16.6	130±16.0**	135±16.0**	141±16.4**	135±16.6	134±17.6	135±15.3
DBP (mmHg)	77±10.0	77±10.0*	77±10.3*	75±9.5*	75±9.9*	77±10.1*	78±9.9*
Nighttime							
SBP (mmHg)	129±19.8	123±18.5**	131±18.9**	137±19.9**	130±20.8	128±19.5	129±19.0
DBP (mmHg)	74±10.7	74±10.5	73±11.2	74±10.4	723±10.8	74±10.5	75±10.8

- 1 EPVS, enlarged perivascular spaces; BG, basal ganglia; WM, white matter; BMI,
- 2 body mass index; CAD, coronary artery atherosclerosis disease; TIA, transient
- 3 ischemic attack; HDL, high-density lipoprotein; LDL, low-density lipoprotein;
- 4 HbA1c, hemoglobin A1c; BUN, blood urea nitrogen, CCB, calcium-channel blocker;

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. \*  $p < 0.05$ , \*\*  $p < 0.01$ .

**Association between ABPV and EPVS in BG**

SD and CV of ambulatory blood pressure in different categories stratified by the degree of EPVS in BG were presented in Table 2. There were statistical differences ( $p < 0.05$ ) among the three subgroups stratified by the severity of EPVS in all of the following BPV metrics: SD and CV of SBP, CV of DBP during 24-hour, daytime and nighttime and SD of DBP during nighttime. These metrics gradually increased with the degree of EPVS increasing (Fig 1-3). The results of spearman correlation analysis demonstrated these metrics were positively associated with the degree of EPVS in BG ( $r > 0$ ,  $P < 0.05$ ) (Table 3). The association between ABPV and EPVS were unchanged even after adjusting for demographic confounders (model 1), Fazekas scale (model 2) and the mean SBP or DBP during the same period (model 3), which indicated that the ABPV were independently associated with EPVS in BG. The results of ordinal logistic regression analysis were presented in Table 4.

**Association between ABPV and EPVS in WM**

SD and CV of ambulatory blood pressure in different categories stratified by degree of EPVS in WM were also presented in Table 2. There were statistical differences ( $p < 0.05$ ) in SD of SBP, CV of SBP, SD of DBP and CV of DBP during 24-hour and daytime among the three categories. However, there were not linear trend among the three subgroups. The results of spearman correlation analysis showed there were no linear correlation between these metrics and the degree of EPVS in WM (Table 3).

**Table 2.** Results of ABPV in all subjects and subgroups stratified by the severity of EPVS

	All patients		EPVS in BG				EPVS in WM			
			Degree 1	Degree 2	Degree 3	P	Degree 1	Degree 2	Degree 3	P
24-hour										
SD of SBP, mmHg	18.28±5.27	16.93±4.76	18.57±4.56	20.13±6.21	<0.001	18.86±5.56	17.36±5.11	18.73±4.99	0.004	

SD of DBP, mmHg	12.56±3.58	12.22±3.56	12.62±3.34	13.05±3.86	0.149	12.83±3.76	11.85±3.32	13.14±3.56	0.001
CV of SBP, %	13.83±3.80	13.21±3.56	13.99±3.54	14.64±4.26	0.004	14.16±3.87	13.23±3.70	14.18±3.76	0.028
CV of DBP, %	16.68±4.74	16.03±4.68	16.82±4.46	17.55±5.04	0.013	17.22±4.76	15.78±4.72	17.14±4.60	0.001
Daytime									
SD of SBP, mmHg	18.02±5.70	16.66±4.93	18.21±5.35	19.99±6.65	<0.001	18.68±5.98	16.99±5.47	18.50±5.49	0.004
SD of DBP, mmHg	12.56±4.01	12.25±3.80	12.51±3.93	13.12±4.40	0.241	12.81±4.06	11.76±3.71	13.26±4.17	0.001
CV of SBP, %	13.45±4.08	12.84±3.75	13.62±4.14	14.26±4.38	0.005	13.86±4.16	12.76±3.88	13.81±4.12	0.016
CV of DBP, %	16.48±5.19	15.84±4.77	16.47±5.24	17.54±5.63	0.024	16.98±4.88	15.47±5.12	17.15±5.48	0.002
Nighttime									
SD of SBP, mmHg	15.21±7.37	13.79±7.71	15.18±5.74	17.54±7.97	<0.001	15.08±6.09	14.94±8.66	15.69±7.05	0.180
SD of DBP, mmHg	10.43±4.50	9.81±4.33	10.77±4.55	11.03±4.61	0.010	10.23±4.11	10.26±4.58	10.88±4.84	0.247
CV of SBP, %	11.85±5.37	11.22±5.53	11.77±4.56	12.95±5.84	0.005	11.69±4.62	11.70±5.95	12.23±5.48	0.411
CV of DBP, %	14.26±6.02	13.42±5.88	14.75±5.89	15.03±6.28	0.003	14.20±5.61	14.08±6.30	14.54±6.17	0.426

1 SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of  
 2 variation; SD: standard deviation.

3 **Table 3.** Results of spearman correlation analysis between the degree of EPVS and  
 4 ABPV

	EPVS in BG		EPVS in WM	
	r	P value	r	P value
24h				
SD of SBP	0.216	0.000	-0.013	0.762
SD of DBP	0.082	0.051	0.030	0.481
CV of SBP	0.137	0.001	-0.008	0.854
CV of DBP	0.123	0.003	-0.028	0.505
Daytime				

SD of SBP	0.205	0.000	-0.024	0.562
SD of DBP	0.065	0.120	0.031	0.459
CV of SBP	0.135	0.001	-0.023	0.585
CV of DBP	0.109	0.009	-0.017	0.679
Nighttime				
SD of SBP	0.229	0.000	0.020	0.637
SD of DBP	0.125	0.003	0.043	0.309
CV of SBP	0.136	0.001	0.027	0.521
CV of DBP	0.135	0.001	0.007	0.870

SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of variation; SD: standard deviation.

**Table 4.** Results of ordinal logistic regression analysis between ABPV and EPVS in BG

	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
24h						
SD of SBP	1.55 (1.32-1.83)	<0.001	1.48 (1.25-1.75)	<0.001	1.41 (1.19-1.68)	<0.001
CV of SBP	1.47 (1.19-1.83)	<0.001	1.48 (1.18-1.85)	0.001	1.60 (1.27-2.02)	<0.001
CV of DBP	1.59 (1.13-2.24)	0.008	1.69 (1.18-2.42)	0.004	1.81 (1.25-2.60)	0.001
Daytime						
SD of SBP	1.44 (1.25-1.67)	<0.001	1.39 (1.19-1.61)	<0.001	1.31 (1.12-1.54)	0.001
CV of SBP	1.32 (1.08-1.61)	0.006	1.32 (1.08-1.62)	0.008	1.43 (1.16-1.77)	0.001
CV of DBP	1.49 (1.10-2.04)	0.011	1.59 (1.15-2.19)	0.005	1.67 (1.21-2.31)	0.002
Nighttime						
SD of SBP	1.29 (1.15-1.46)	<0.001	1.25 (1.11-1.40)	<0.001	1.21 (1.07-1.37)	0.002
SD of DBP	1.39 (1.15-1.67)	<0.001	1.33 (1.11-1.61)	0.003	1.31 (1.12-1.54)	0.001
CV of SBP	1.27 (1.09-1.48)	0.002	1.26 (1.08-1.47)	0.003	1.31 (1.08-1.58)	0.006
CV of DBP	1.19 (1.04-1.36)	0.013	1.20 (1.04-1.37)	0.012	1.21 (1.05-1.39)	0.008

Results of ordinal regression analysis presented as OR per 5% increase in CV of

1 blood pressure and 5 mmHg in SD of blood pressure.

2 Model1: adjusted for age, smoking, alcohol, hypertension, stroke/TIA, BUN,  
3 creatinine and using of anti-hypertensive drugs.

4 Model2: model 1 + Fazekas scale.

5 Model3: model 2 + the mean SBP or DBP during the same period.

## 6 **DISCUSSION**

7 In this study, we explored the relationship between ABPV and EPVS based on the  
8 population who presented for physical exam. Our data suggested that all of the  
9 following metrics: SD of SBP, CV of SBP and CV of DBP during 24-hour, daytime  
10 and nighttime and SD of DBP during nighttime were positively associated with the  
11 degree of EPVS in BG. The association between the above ABPV metrics and EPVS  
12 in BG were unchanged after adjusting for demographic confounders, Fazekas scale  
13 and the mean SBP or DBP during the same period. Although there were statistical  
14 differences in ABPV metrics during 24-hour and daytime among the three subgroups  
15 stratified by EPVS severity in WM, there were no linear correlation between ABPV  
16 and the degree of EPVS in WM. In addition, we found age, Fazekas scale,  
17 hypertension, stroke/transient ischemic attack (TIA), levels of blood urea nitrogen and  
18 creatinine were positively associated with the degree of EPVS in BG.

19 There were methodological strengths of our study. We recruited participants strictly  
20 according to inclusion and exclusion criteria to avoid selection bias. The patients with  
21 acute cerebrovascular and cardiovascular disorders were excluded to avoid the impact  
22 of the acute stroke, recent myocardial infarction or angina pectoris on blood pressure.  
23 The patients with a history of severe ischemic (the largest diameter of infarct size >  
24 20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or  
25 hemorrhagic stroke were excluded because of difficulty and inaccurate assessment on  
26 EPVS. In addition, the assessments of EPVS and WMH were performed by two  
27 experienced neurologists blinded to clinical information and disagreements were  
28 resolved by consensus, which ensure the accuracy of the assessments. We collected  
29 detailed information on vascular confounders, WMH, levels of blood urea nitrogen  
30 and creatinine, which are crucial to the interpretation of EPVS<sup>6, 21</sup>. So we think the



1 reliability of the data is high. There were some limitations in our study. First, our  
2 study was based on a population who visited the hospital for physical exam in a single  
3 center and the cohort may not represent the general population. According to our  
4 observation, these people had a higher economic status than that of the general  
5 population in China, and some of them showed more symptoms of anxiety. But it's  
6 regrettable that we didn't assess the anxiety symptoms by the Hamilton Anxiety  
7 Rating Scale or assess the patients' education level. Second, this was a cross-sectional  
8 study, and the causal relationship between ABPV and EPVS could not be established.  
9 Third, all participants underwent 24-hour ABPM which could only show short-term  
10 ABPV. It has been demonstrated that the prognostic significance of BPV on vascular  
11 diseases is weaker for short-term than for long-term BPV<sup>22</sup>.  
12 This is the first study to investigate the relationship between ABPV and EPVS.  
13 Previously, several studies investigated the relationship between EPVS and  
14 hypertension. In a prospective, multicenter, hospital-based study, Zhang CQ et al<sup>19</sup>  
15 found hypertension was associated with the severity of EPVS in WM, not in BG.  
16 Klarenbeek P et al<sup>23</sup> investigated the association between ABP levels and EPVS in  
17 first-ever lacunar stroke patients. They found higher day systolic, day diastolic and  
18 24-hour diastolic BP levels were independently associated EPVS in BG, and no  
19 relation between ABP levels and EPVS in WM. We also analyzed the correlation  
20 between ABP levels and EPVS. We found ABP levels were associated with EPVS in  
21 BG, but not in WMH, which is consistent with Klarenbeek P et al.'s study. However,  
22 we found only SBP was positively related to higher degree of EPVS in BG in all  
23 periods, and no relation between DBP and EPVS, which are different from previous  
24 results. The different study population and different scoring methods of assessing  
25 EPVS may partly lead to the different results. Our data suggested that SD of SBP, CV  
26 of SBP and CV of DBP in all periods were positively associated with the degree of  
27 EPVS in BG, but not in WM. The present study couldn't explain the phenomenon.  
28 This may be caused by different pathogenesis of EPVS at the different locations<sup>18, 19,</sup>  
29 <sup>24</sup>. Previous studies have found the anatomical structure of EPVS located in BG and  
30 WM were different<sup>25</sup>. The arteries in the basal ganglia are surrounded by 2 distinct

coats of leptomeninges separated by a perivascular space which is continuous with the perivascular space around arteries in the subarachnoid space. Whereas there are only single periarterial layer of leptomeninges surrounding the arteries in the cerebral cortex and they penetrate into the white matter. Drainage of interstitial fluid from the brain to cervical lymph nodes may mainly go along perivascular spaces in WM rather than in BG<sup>3, 26</sup>. In addition, the impact of age, hypertension on EPVS seems to be stronger for EPVS located in BG than for those located in WM<sup>18</sup>. Similarly, the association between EPVS and the load of WMH, taken as a marker of CSVD, also appears to be stronger in BG than in WM. Thus, their dilations may present differences in terms of risk factors as well as in mechanisms in BG and WM. However, the reason SBP is related differently in these two locations remains unclear because there are a very limited number of studies on mechanisms underlying dilation of perivascular spaces in BG and WM. Several studies have demonstrated higher ABPV increased the risk of neuroimaging features of CSVD, such as WMH and lacunar infarction<sup>14, 15</sup>. Our results found higher ABPV was independently associated with higher degree of EPVS in BG, which support the finding that EPVS in BG are a separate marker of CSVD.

An increased permeability of the small vessel walls and blood brain barrier (BBB) are considered to contribute to the development of EPVS, which has been reported to be associated with damage of microvascular endothelial cells and their tight junctions<sup>1, 16, 27</sup>. Higher ABPV would lead to more mechanical stress on the wall vessel, endothelial injury<sup>28</sup> and arterial stiffness<sup>29</sup>. Therefore, it is reasonable that high ABPV contribute to the development of EPVS by damaging endothelial cells. Our results may remind clinicians that they should pay attention to patients' ABPV and lower patients' ABPV in their clinical practices. In the future, a prospective cohort study will help better establish the relationship between ABPV and EPVS.

## CONCLUSION

SD of SBP, CV of SBP and CV of DBP during all periods and SD of DBP during nighttime were positively associated with the degree of EPVS in BG. The association was unchanged after adjusting for confounders. No relation was found between ABPV

1 and EPVS in WM. It is important for clinicians to reduce both patients' high blood  
2 pressure levels and ABPV.

3 **Contributors** WH conceived and designed the experiments. SY, WQ, LY and HF  
4 participated in the data collection. JY and YL participated in the analysis of the data.  
5 SY drafted the manuscript. WH has given final approval of the version to be  
6 published. All authors read and approved the final manuscript.

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9 **Conflict of Interest** None declared.

10 **Ethic approval** The study was approved by the Ethics Committee of Beijing  
11 Chaoyang Hospital Affiliated to Capital Medical University and was performed in  
12 accordance with the declaration of Helsinki.

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15 **Data sharing statement** No additional data are available.

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29 **Figure 1.** The ABPV metrics of subgroups stratified by EPVS severity in BG during

30 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD

31 of systolic blood pressure. (d) SD of diastolic blood pressure.

32 **Figure 2.** The ABPV metrics of subgroups stratified by EPVS severity in BG during

33 daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD

34 of systolic blood pressure. (d) SD of diastolic blood pressure.

35 **Figure 3.** The ABPV metrics of subgroups stratified by EPVS severity in BG during

36 nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c)

37 SD of systolic blood pressure. (d) SD of diastolic blood pressure.

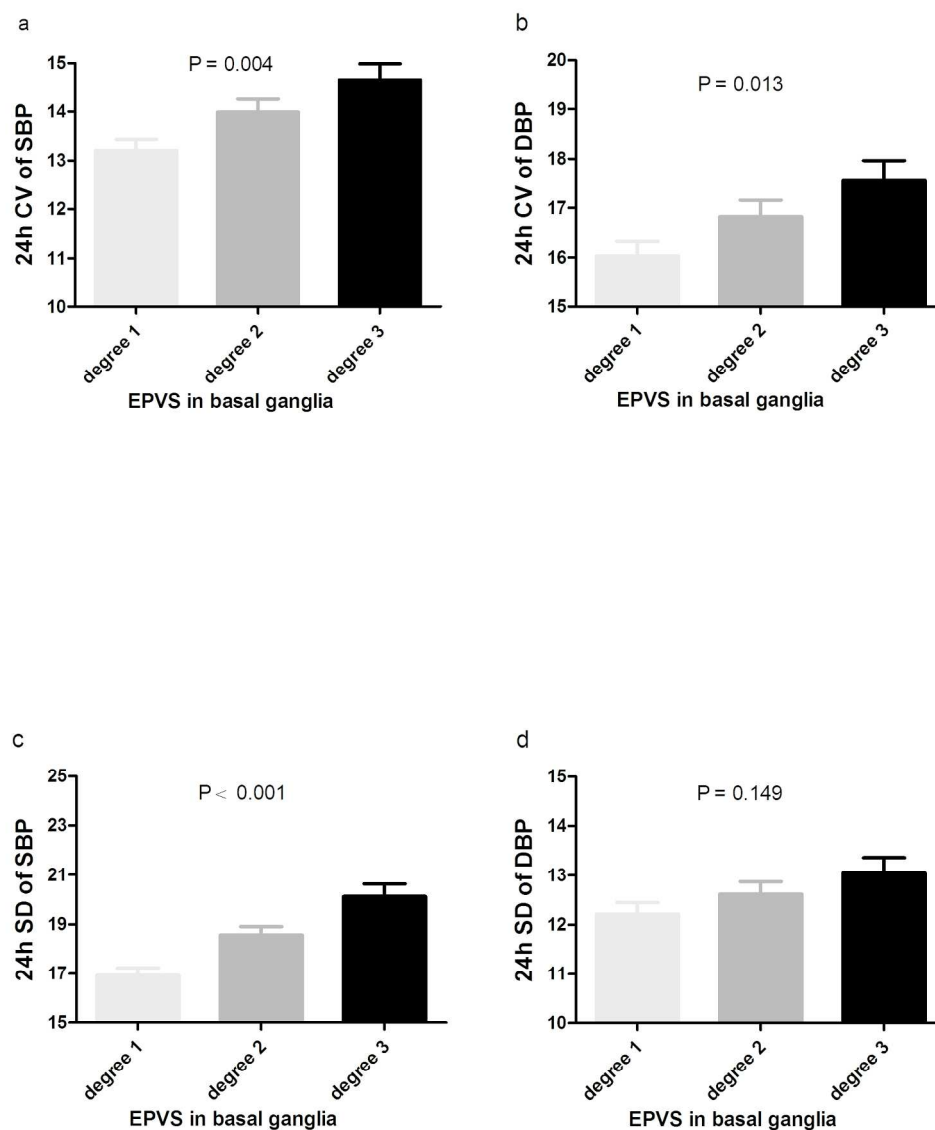


Figure 1. The ABPV metrics of subgroups stratified by EPVS severity in BG during 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

191x228mm (300 x 300 DPI)

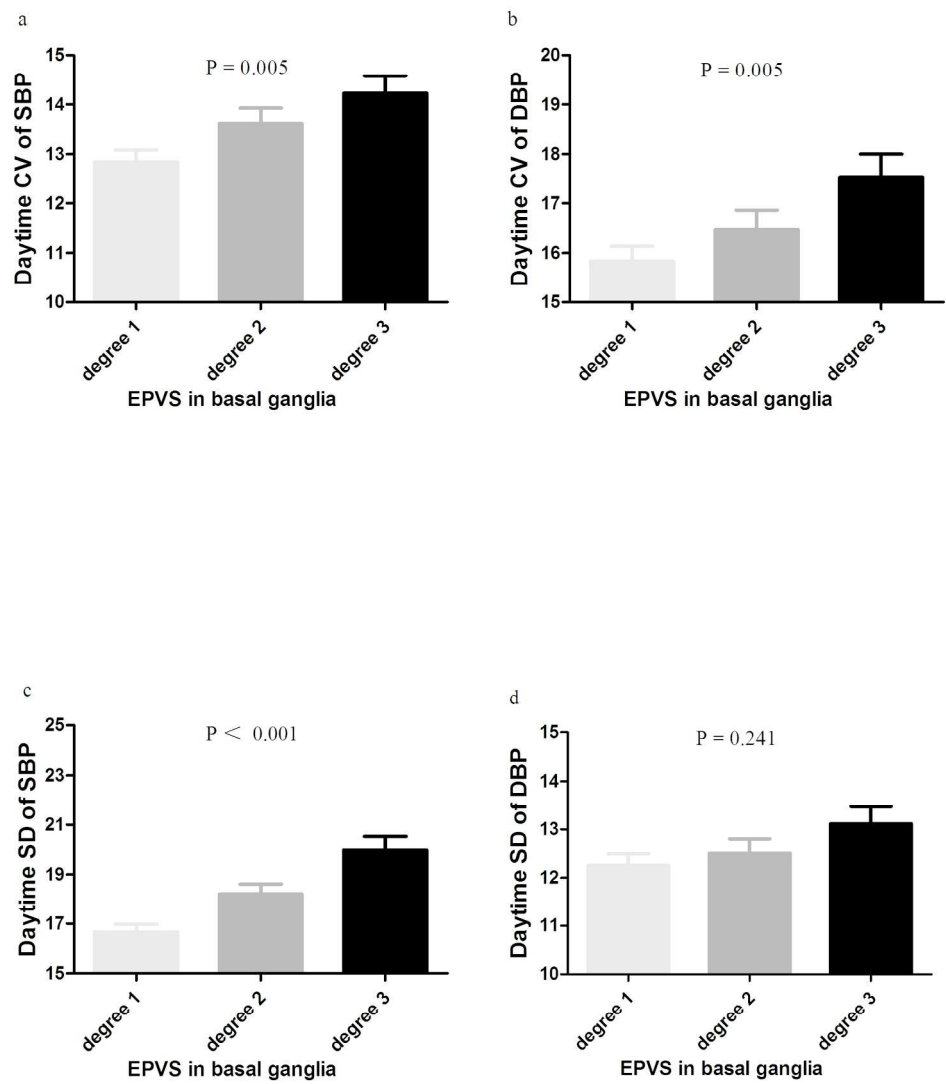


Figure 2. The ABPV metrics of subgroups stratified by EPVS severity in BG during daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

190x218mm (300 x 300 DPI)



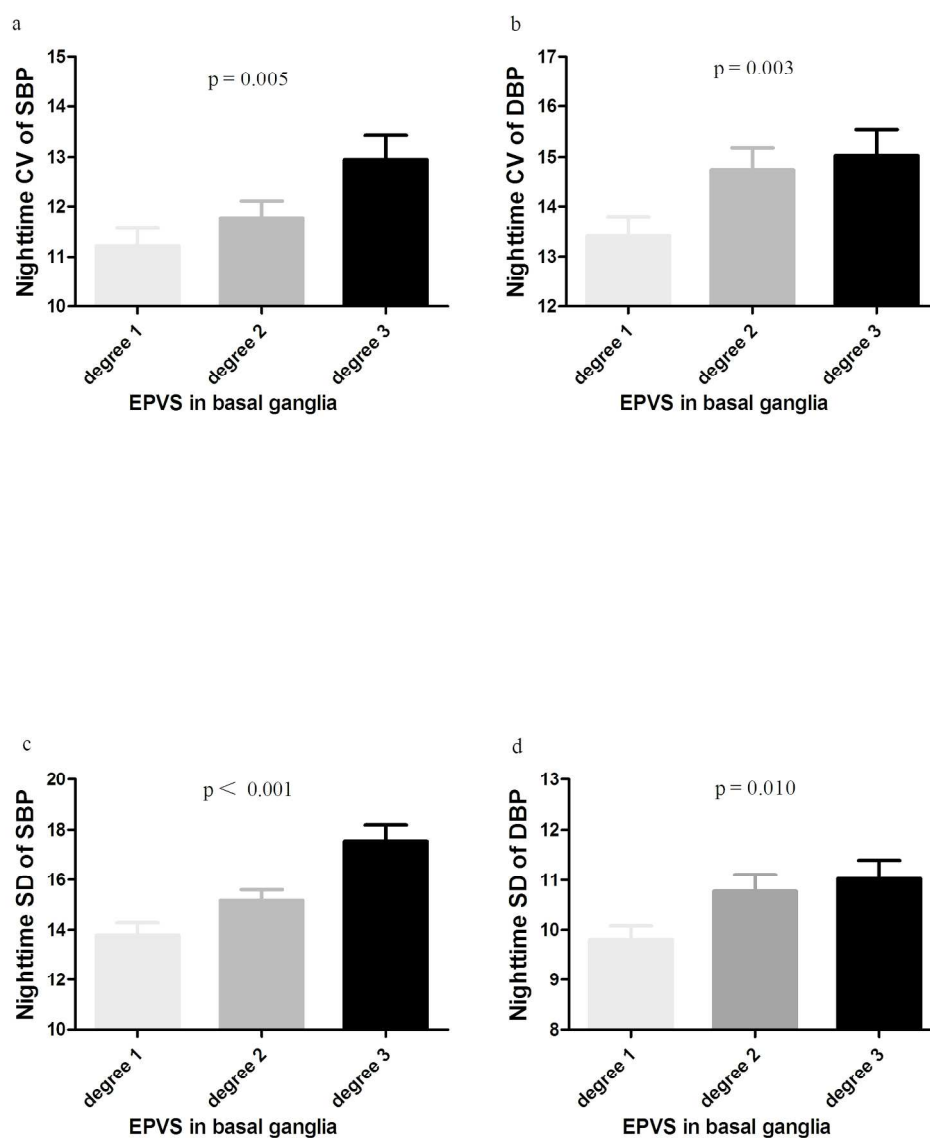


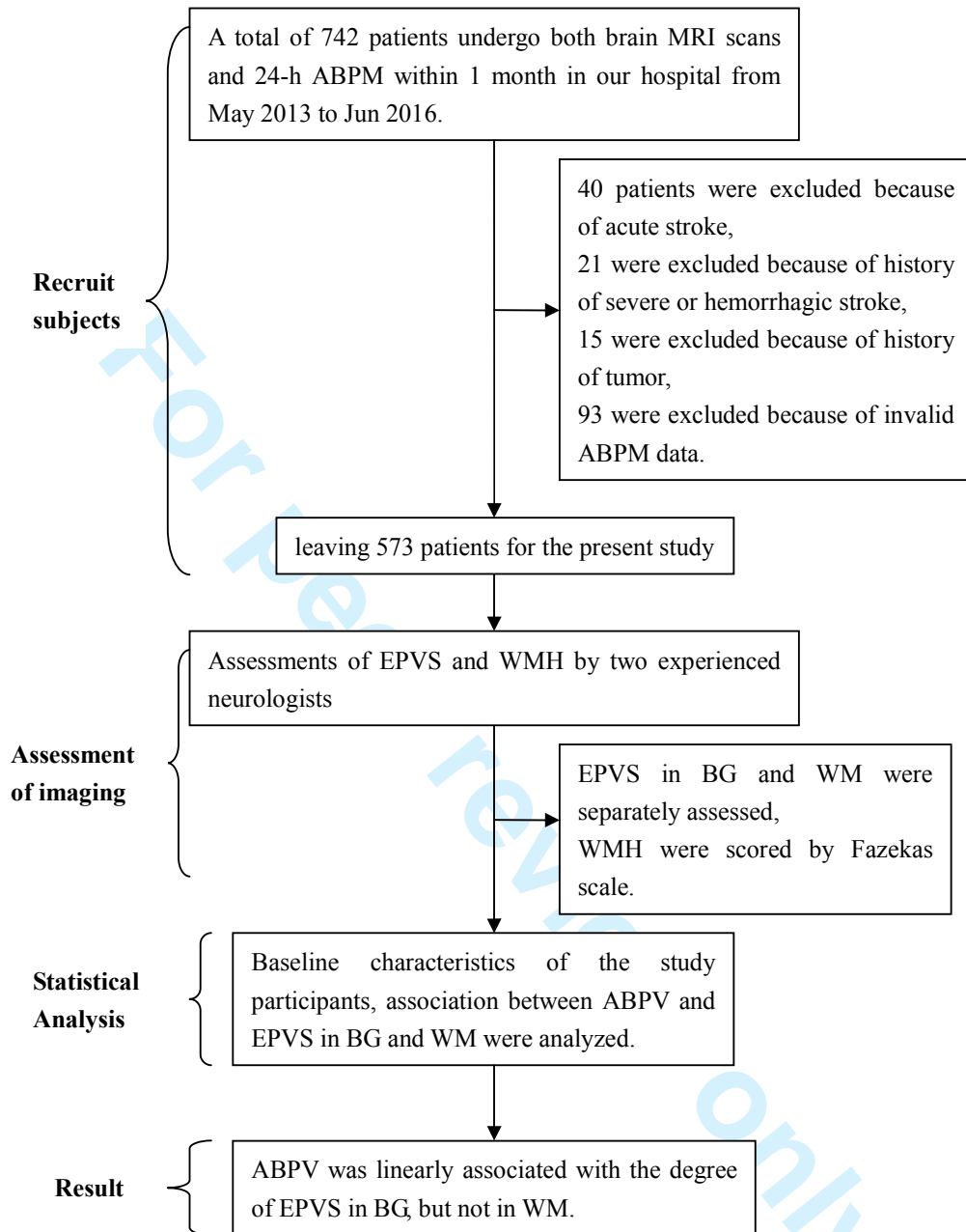
Figure 3. The ABPV metrics of subgroups stratified by EPVS severity in BG during nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

189x227mm (300 x 300 DPI)



The comparison of general clinical characteristics between the included and excluded participants

Characteristics	enrolled patients	excluded patients	P
n	573	169	-
Age, years	67.8±14.8	69.6±9.6	0.443
Sex, male (%)	355 (62.0)	101(59.8)	0.607
Current smoking (%)	162 (28.3)	55(32.5)	0.283
Current alcohol (%)	126 (22.0)	42(24.9)	0.435
Hypertension (%)	420 (73.3)	115(68.0)	0.181
Diabetes (%)	191 (33.3)	44(26.0)	0.073
coronary atherosclerosis disease (%)	140 (24.4)	35(20.7)	0.316
body mass index, kg/m <sup>2</sup>	25.6±3.5	25.1±3.0	0.160
Using of anti-hypertensive drugs (%)	342 (59.7)	99(58.6)	0.797



ABPM, ambulatory blood pressure monitoring; EPVS, enlarged perivascular spaces; WMH, white matter hyperintensities; BG, basal ganglia; WM, white matter.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	P1 and 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	P2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	P4
Methods			
Study design	4	Present key elements of study design early in the paper	P4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	P4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P5-6
Bias	9	Describe any efforts to address potential sources of bias	P4 and 5

Study size	10	Explain how the study size was arrived at	P4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	P6
		(b) Describe any methods used to examine subgroups and interactions	P6
		(c) Explain how missing data were addressed	P6
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P6
		(b) Give reasons for non-participation at each stage	P6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P7
		(b) Indicate number of participants with missing data for each variable of interest	P7
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P6-12
		(b) Report category boundaries when continuous variables were categorized	

		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	P12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	P14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P15

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

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**1     The relationship between ambulatory blood pressure variability and**  
**2     enlarged perivascular spaces: a cross-sectional study**

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## Abstract

**Objectives:** Recent studies reported that 24-hour ambulatory blood pressure variability (ABPV) was associated with lacunar infarction and white matter hyperintensities (WMH). However, the relationship between ABPV and enlarged perivascular spaces (EPVS) hasn't been investigated. Thus, our study aimed to investigate whether ABPV is associated with EPVS by 24-hour ambulatory blood pressure monitoring (ABPM).

**Design:** We conducted this study as a cross-sectional study.

**Settings:** The study was based on patients who presented for physical examinations in our hospital from May 2013 to Jun 2016.

**Participants:** Patients with both brain MRI scans and 24-hour ABPM were included and patients with acute stroke, a history of severe stroke and some other severe diseases were excluded. A total of 573 Chinese patients were prospectively enrolled in this study.

**Primary and secondary outcome measures:** EPVS in basal ganglia (BG) and white matter (WM) were identified on MRI and classified into three categories by the severity. WMH were scored by Fazekas scale. Coefficient of variation (CV) and standard deviation (SD) were considered as metrics of ABPV. Spearman correlation analysis and ordinal logistic regression analysis were used to assess the relationship between ABPV and EPVS.

**Results:** There were statistical differences among the subgroups stratified by the severity of EPVS in BG in the following ABPV metrics: SD and CV of systolic blood pressure (SBP), CV of diastolic blood pressure (DBP) in 24-hour, daytime and nighttime and SD of DBP in nighttime. The above ABPV metrics were positively associated with the degree of EPVS. The association was unchanged after adjusting for confounders. Spearman correlation analysis showed ABPV wasn't related to the degree of EPVS in WM.

**Conclusion:** ABPV was independently associated with EPVS in BG after controlling for blood pressure, but not in WM. Pathogenesis of EPVS in BG and WM might be different.



**Keywords** cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

**Strengths and limitations of this study**

- Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments.
- Detailed information on some confounders crucial to the interpretation of EPVS was collected and ordinal logistic regression analysis was performed to determine the independency of association.
- The study was based on a population who presented to the hospital for physical exam in a single center and the cohort may not represent the general population.
- This was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established.

**INTRODUCTION**

Perivascular spaces, or Virchow-Robin spaces, are perivascular compartments surrounding the small penetrating cerebral vessels, serving as an important drainage system for interstitial fluids and solute in the brain<sup>1</sup>. They can dilate with accumulation of the interstitial fluids<sup>2, 3</sup>. Enlarged perivascular spaces (EPVS) appear as punctate or linear signal intensities similar to cerebrospinal fluids (CSF) on all MRI sequences in white matter (WM), basal ganglia (BG), hippocampus and brainstem<sup>4, 5</sup>. Recent studies indicated that EPVS were a magnetic resonance imaging (MRI) marker of cerebral small vessel diseases (CSVD) and were associated with other morphological features of CSVD such as white matter hyperintensities (WMH) and lacunes<sup>6, 7</sup>. Some studies found EPVS were associated with impaired cognitive function<sup>5</sup>, incident dementia<sup>8</sup> and sleep disorders<sup>9</sup>. Therefore, it is of clinical importance to understand the risk factors for EPVS and search for treatable options in the future.

24-hour ambulatory blood pressure monitoring (ABPM) is proven to be a more useful and scientific method to predict blood pressure-related brain damage than single

office blood pressure measurement<sup>10, 11</sup>. Ambulatory blood pressure variability (ABPV) could be well documented by 24-hour ABPM. Previous studies demonstrated higher ABPV increased the risk of cardiovascular events<sup>12, 13</sup>, WMH, lacunar infarction, and cognitive decline<sup>14, 15</sup>. WMH, lacunar infarction and EPVS are all neuroimaging features of CSVD and share some risk factors, such as age and hypertension<sup>16</sup>. However, the relationship between ABPV and EPVS has never been investigated. Thus in the present study, we aimed to investigate whether ABPV, which was reflected by 24-hour ABPM, was independently associated with EPVS.

## METHODS

### Study subjects

We conducted this study as a cross-sectional study. The inpatients for physical examinations in Medicine Department and Neurology Department of Beijing Chaoyang Hospital Affiliated to Capital Medical University were prospectively identified from May 2013 to Jun 2016. Some of them had a history of hypertension, diabetes mellitus, lacunar stroke or other risk factors for vascular diseases. They worried about the cerebrovascular diseases and wanted a well check up. They were screened according to our inclusion and exclusion criteria. The number of arriving patients during the study period, inclusion and exclusion criteria determined the sample size. Inclusion criteria were: (1) patients underwent both brain MRI scans and 24-hour ABPM within 1 month; (2) patients agreed to participate in our study and signed an informed consent. The following patients were excluded: (1) patients with acute stroke, Parkinson disease, dementia, severe traumatic or toxic or infectious brain injury, and brain tumor; (2) patients with severe heart disease, recent myocardial infarction or angina pectoris disorders, severe infections, severe nephrosis or liver disease, thrombotic diseases and tumor; (3) patients with history of severe ischemic (the largest diameter of infarct size > 20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke because of difficulty assessments on EPVS; (4) patients with invalid 24-hour ABPM data (The 24-h ABPM data were considered invalid if measurement times was < 70%, or < 1

1 measurement per hour during daytime, or < 6 in total during nighttime).

2 **Assessments of EPVS and WMH**

3 The neurological image examinations were performed in Radiology Department of  
4 our hospital. MR images were acquired on a 3.0 T MR scanner (Siemens, Erlangen,  
5 Germany).

6 EPVS were defined as CSF-like signal intensity lesions of round, ovoid, or linear  
7 shape of < 3mm and located in areas supplied by perforating arteries<sup>6, 17</sup>. We  
8 distinguished lacune from EPVS by their larger size (> 3mm), spheroid shape and  
9 surrounding hyperintensities on FLAIR. WMH were defined as hyperintense signals  
10 on T2-weighted and FLAIR and decreased signal intensities on T1-weighted MR  
11 imaging.

12 EPVS in BG and WM were separately assessed according to the scales which were  
13 used in other studies<sup>18</sup>. In BG, EPVS were rated according to the number in the slice  
14 containing the maximum amount of EPVS. The grades of EPVS were rated as  
15 following: grade 1: < 5 EPVS, grade 2: 5 to 10 EPVS, grade 3: 10 to 20 EPVS, and  
16 grade 4: > 20 EPVS. In WM, EPVS were scored as follows: grade 1: <10 EPVS in  
17 total WM, grade 2: >10 in total WM and <10 in the slice containing the maximum  
18 number of EPVS, grade 3: 10 to 20 EPVS in the slice containing the maximum  
19 number of EPVS, grade 4: > 20 in the slice containing the maximum number of EPVS.  
20 We classified EPVS into three categories: degree 1 = grade 1; degree 2 = grade 2;  
21 degree 3 = grade 3 and 4.

22 WMH were scored by Fazekas scale. The detailed description of assessments has  
23 been previously published<sup>19</sup>. Periventricular and deep WMH were evaluated  
24 separately and then added together as Fazekas scores.

25 The intrarater agreement for the rating of EPVS and WMH was assessed on a random  
26 sample of 100 individuals with a month interval between the first and second readings.  
27 Assessments of EPVS and WMH were performed by two experienced neurologists  
28 blinded to clinical information to avoid bias. Random scans of 100 individuals were  
29 independently examined by the two experienced neurologists blinded to each other's  
30 readings. The *k* statistics of intrarater and interrater agreement was 0.80 or above,

1 indicating good reliability. Disagreement was resolved by discussing with other  
2 co-authors.

### 3 **24-hour ambulatory blood pressure monitoring**

4 24-hour ABPM was performed using an automated system (FB-250; Fukuda Denshi,  
5 Tokyo, Japan). BP was measured every 30 minutes during the daytime (8:00 AM to  
6 11:00 PM) and every 60 minutes during the nighttime (11:00 PM to 8:00 AM). We  
7 excluded a 2-hour transition period around the reported rising and retiring times. The  
8 mean systolic blood pressure (SBP), diastolic blood pressure (DBP), coefficient of  
9 variation (CV) and standard deviation (SD) of SBP and DBP during 24-hour, daytime,  
10 and nighttime were collected. The CV value was defined as the ratio between the SD  
11 and the mean SBP or DBP at the same periods. SD and CV were considered as  
12 metrics of BPV in this study. Patients continued taking their previous medications,  
13 and we registered the use of anti-hypertension drugs.

### 14 **Statistical analysis**

15 Continuous variables were summarized as mean values  $\pm$  standard deviation (SD) or  
16 median (interquartile range) according to whether its distribution conformed to a  
17 normal distribution. Analysis of variance (ANOVA) was used for comparison of  
18 continuous variables with both normal distribution and homogeneity of variance,  
19 whereas were compared with Kruskal–Wallis test as appropriate. Categorical  
20 variables were presented as absolute numbers and percentages. Chi-squared test was  
21 used for comparison of categorical variables. Spearman correlation analysis was used  
22 to calculate the association between ABPV and the severity of EPVS. The  
23 proportional odds assumption was met, thus ordinal logistic regression analysis was  
24 performed to determine whether the ABPV was independently associated with EPVS  
25 after adjusting for demographic confounders (model 1), Fazekas scale (model 2) and  
26 the mean SBP or DBP during the same period (model 3). The results were based on  
27 valid data; missing data were excluded. Analyses were performed with Statistical  
28 Package for Social Sciences (SPSS version21.0), and statistical significance was  
29 accepted at the  $p < 0.05$ .

### 30 **RESULTS**

**Baseline characteristics of the study participants**

742 patients underwent both brain MRI scans and 24-hour ABPM within 1 month in the Medicine Department or Neurology Department of our hospital from May 2013 to Jun 2016. 40 patients were excluded because of acute stroke, 21 were excluded because of history of severe or hemorrhagic stroke, 15 were excluded because of a history of tumor and 93 were excluded because of invalid ABPM data, leaving 573 patients enrolled in the present study. None of them had missing data. There were no statistical differences ( $P>0.05$ ) in age, body mass index, proportion of male, current smoking, current alcohol, diabetes, hypertension, coronary artery atherosclerosis disease and using of anti-hypertensive drugs between the excluded subjects and the final group (Supplementary file). Table 1 showed the characteristics of all enrolled subjects and subgroups stratified by the degree of EPVS in different brain regions. Age, Fazekas scale, proportion of hypertension and stroke/TIA, levels of blood urea nitrogen and creatinine increased with the degree of EPVS in BG increasing. There were statistical differences in age, Fazekas scale and proportion of coronary artery atherosclerosis disease (CAD) among subgroups based on the degree of EPVS in WM.

There were statistical differences in the mean SBP during 24-hour, daytime, and nighttime among the categories stratified by the degree of EPVS in BG. The results of spearman correlation analysis showed SBP was positively related to higher degree of EPVS in BG during all periods (SBP of 24-hour:  $r=0.23$ ,  $p < 0.01$ ; SBP of daytime:  $r=0.25$ ,  $p < 0.01$ ; SBP of nighttime:  $r=0.30$ ,  $p < 0.01$ ). The mean DBP of daytime and nighttime increased with the degree of EPVS in WMH increasing. However, the results of spearman correlation analysis showed that DBP levels were not associated with higher numbers of EPVS in WM ( $p > 0.05$ ).

**Table 1.** General characteristics of all enrolled subjects and subgroups stratified by the severity of EPVS

Characteristics	All patients	EPVS in BG			EPVS in WM		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3

n (%)	573	244 (42.6%)	179 (31.2%)	150 (26.2%)	200 (34.9%)	207 (36.1%)	166 (29.0%)
Age, <sup>a</sup> years	69(55-81)	58(51-74)**	68(57-80)**	80(73-85)**	75(57-83)**	66(55-78)**	66(54-80)**
Sex, male (%)	355 (62.0)	143 (58.6)	108 (60.3)	104 (69.3)	115 (57.5)	128 (61.8)	112 (67.5)
Current smoking (%)	162 (28.3)	83 (34.0)*	61(34.1)*	18(12.0)*	52 (26.0)	60 (29.0)	50 (30.1)
Current alcohol (%)	126 (22.0)	62 (25.4)*	45 (25.1)*	19 (12.7)*	36 (18.0)	50 (24.2)	40 (24.1)
Hypertension (%)	420 (73.3)	170 (69.7)*	122 (68.2)*	128 (85.3)*	150 (75.0)	145 (70.5)	125 (74.7)
Diabetes (%)	191 (33.3)	78 (32.0)	59 (33.0)	54 (36.0)	71 (35.5)	62 (30.0)	58 (34.9)
CAD (%)	140 (24.4)	48 (19.7)	48 (26.8)	44 (29.3)	61 (30.5) *	45 (21.7) *	34 (20.5) *
Stroke or TIA (%)	125 (21.8)	40 (16.4)**	33 (18.4)**	52 (34.7)**	49 (24.5)	39 (18.8)	37 (22.2)
BMI, <sup>b</sup> kg/m <sup>2</sup>	25.6±3.5	25.6±3.4	25.3±3.5	25.8±3.5	25.8±3.4	25.4±3.5	25.5±3.5
HDL, <sup>a</sup> mmol/L	1.16(1.00-1.38)	1.15(0.99-1.37)	1.17(0.98-1.41)	1.17(1.00-1.32)	1.17(1.00-1.38)	1.15(0.98-1.37)	1.15(0.99-1.34)
LDL, <sup>a</sup> mmol/L	2.40(1.90-2.94)	2.42(1.96-3.00)	2.47(1.88-2.93)	2.20(1.79-2.91)	2.32(1.88-2.94)	2.29(1.81-2.90)	2.51(2.00-3.00)
HbA1c, <sup>a</sup> %	6.0(5.7-6.7)	6.0(5.7-6.7)	6.0(5.7-6.7)	6.1(5.7-6.7)	6.1(5.7-6.8)	6.0(5.7-6.6)	6.0(5.7-6.8)
BUN, <sup>a</sup> mmol/L	5.46(4.46-6.70)	5.18(4.34-6.34)**	5.36(4.32-6.59)**	5.97(4.82-7.42)**	5.50(4.55-7.02)	5.39(4.36-6.39)	5.42(4.50-6.81)
Creatinine, <sup>a</sup> μmol/L	74.2(62.8-89.2)	70.2(59.7-84.6)**	74.5(63.7-89.6)**	81.9(66.4-94.1)**	77.0(62.8-92.1)	72.5(61.5-87.0)	74.0(62.9-89.1)
Fazekas scale <sup>a</sup>	3(2-5)	2(1-3)**	3(2-4)**	5(4-6)**	3(2-6)**	2(2-4)**	3(2-4)**
Using of anti-hypertensive drugs	342 (59.7)	130 (53.3) *	96 (53.6) *	116 (77.3) *	129 (64.5)	114 (55.1)	99 (59.6)
(%)							
Class of anti-hypertensive drugs							
Dihydropyridinic CCB (%)	226 (39.4)	74 (30.3)	67 (37.4)	63 (42.0)	69 (34.5)	79 (38.2)	55 (33.1)
ACEI (%)	26 (4.5)	11 (4.5)	6 (3.4)	9 (6.0)	8 (4.0)	9 (4.3)	9 (5.7)
ARB (%)	160 (27.9)	70 (28.7)	46 (25.7)	44 (29.3)	69 (34.5) *	52 (25.1) *	39 (23.5) *
β-Blockers (%)	96 (16.8)	34 (13.9)	28 (15.6)	34 (22.7)	40 (20.0)	31 (15.0)	25 (15.1)
Nonloop diuretics (%)	39 (6.8)	20 (8.2)	12 (6.7)	7 (4.7)	16 (8.0)	13 (6.3)	10 (6.0)
24-hour							
SBP, <sup>a,b</sup> mmHg	132(121-143)	127(117-138)**	133(124-143)**	136(127-148)**	133±16.5	132±17.1	132.9±15.4
DBP, <sup>b</sup> mmHg	76±9.6	77±9.5	76±10.0	75±9.1	75±9.5*	76±9.6*	77±9.6*
Daytime							
SBP, <sup>a,b</sup> mmHg	134(123-145)	129(118-141)**	135(126-144)**	140(130-150)**	135±16.6	134±17.6	135±15.3

DBP, <sup>b</sup> mmHg	77±10.0	77±10.0*	77±10.3*	75±9.5*	75±9.9*	77±10.1*	78±9.9*
Nighttime							
SBP, <sup>a</sup> mmHg	126(116-142)	120(110-134)**	131(118-142)**	135(123-149)**	127(115-144)	124(113-140)	128(117-142)
DBP, <sup>a</sup> mmHg	73(66-80)	74(66-81)	73(66-81)	73(67-80)	71(65-79)	73(66-80)	75(68-82)

1 EPVS, enlarged perivascular spaces; BG, basal ganglia; WM, white matter; BMI,  
2 body mass index; CAD, coronary artery atherosclerosis disease; TIA, transient  
3 ischemic attack; HDL, high-density lipoprotein; LDL, low-density lipoprotein;  
4 HbA1c, hemoglobin A1c; BUN, blood urea nitrogen, CCB, calcium-channel blocker;  
5 ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. \*  
6  $p < 0.05$ , \* \*  $p < 0.01$ .

7 <sup>a</sup>: Continuous variables with non normally distribution were expressed as median  
8 (interquartile range) and compared with Kruskal–Wallis test. <sup>b</sup>: Continuous variables  
9 with normal distribution were expressed as mean values ± standard deviation, but with  
10 heterogeneity of variance, thus were compared with Kruskal–Wallis test.

11 **Association between ABPV and EPVS in BG**

12 SD and CV of ambulatory blood pressure in different categories stratified by the  
13 degree of EPVS in BG were presented in Table 2. There were statistical differences ( $p$   
14  $< 0.05$ ) among the three subgroups stratified by the severity of EPVS in all of the  
15 following BPV metrics: SD and CV of SBP, CV of DBP during 24-hour, daytime and  
16 nighttime and SD of DBP during nighttime. Theses metrics gradually increased with  
17 the degree of EPVS increasing (Fig 1-3). The results of spearman correlation analysis  
18 demonstrated theses metrics were positively associated with the degree of EPVS in  
19 BG ( $r > 0$ ,  $P < 0.05$ ) (Table 3). The association between ABPV and EPVS were  
20 unchanged even after adjusting for demographic confounders (model 1), Fazekas  
21 scale (model 2) and the mean SBP or DBP during the same period (model 3), which  
22 indicated that the ABPV were independently associated with EPVS in BG. The results  
23 of ordinal logistic regression analysis were presented in Table 4.

24 **Association between ABPV and EPVS in WM**

25 SD and CV of ambulatory blood pressure in different categories stratified by degree  
26 of EPVS in WM were also presented in Table 2. There were statistical differences ( $p <$



0.05) in SD of SBP, CV of SBP, SD of DBP and CV of DBP during 24-hour and daytime among the three categories. However, there were not linear trend among the three subgroups. The results of spearman correlation analysis showed there were no linear correlation between these metrics and the degree of EPVS in WM (Table 3).

**Table 2.** Results of ABPV in all subjects and subgroups stratified by the severity of EPVS

	EPVS in BG				EPVS in WM			
	Degree 1	Degree 2	Degree 3	P	Degree 1	Degree 2	Degree 3	P
24-hour								
SD of SBP, <sup>a</sup> mmHg	16.6(13.8-20.2)	18.1(15.1-21.5)	18.8(15.5-23.9)	<0.001	18.2(14.7-22.8)	16.9(13.7-20.2)	17.7(15.0-21.7)	0.004
SD of DBP, <sup>a</sup> mmHg	11.8(9.8-14.3)	12.2(10.1-15.2)	12.5(10.1-15.3)	0.149	12.7(10.1-14.5)	11.4(9.4-14.1)	12.7(10.7-15.5)	0.001
CV of SBP, <sup>a</sup> %	12.9(10.4-15.3)	13.6(11.4-16.2)	14.4(11.2-17.4)	0.004	13.6(11.3-16.5)	13.2(10.3-15.5)	13.5(11.5-16.5)	0.028
CV of DBP, <sup>a</sup> %	15.4(12.9-19.0)	16.1(13.5-19.9)	17.3(13.8-20.2)	0.013	17.1(13.9-19.8)	15.0(12.4-18.4)	16.6(13.8-19.9)	0.001
Daytime								
SD of SBP, <sup>a</sup> mmHg	16.2(13.2-19.8)	17.1(14.2-21.5)	18.7(14.8-25.0)	<0.001	18.2(14.1-22.6)	16.3(13.2-19.7)	17.2(14.3-22.6)	0.004
SD of DBP, <sup>a</sup> mmHg	11.7(9.6-14.8)	11.8(9.5-15.0)	12.7(9.8-15.7)	0.241	12.2(9.7-15.3)	11.3(8.8-13.6)	12.6(10.2-16.0)	0.001
CV of SBP, <sup>a</sup> %	12.2(10.1-15.1)	12.9(10.8-16.1)	13.9(10.8-17.5)	0.005	13.3(10.6-16.7)	12.3(9.8-15.1)	13.1(10.5-16.6)	0.016
CV of DBP, <sup>a</sup> %	15.3(12.2-19.4)	15.1(12.7-20.5)	17.1(13.5-20.4)	0.024	16.4(13.3-20.3)	14.8(11.7-19.1)	16.3(13.2-20.4)	0.002
Nighttime								
SD of SBP, <sup>a</sup> mmHg	12.5(9.5-16.4)	14.8(11.0-19.0)	16.5(11.3-22.6)	<0.001	13.5(10.9-18.6)	13.4(9.8-18.9)	15.2(10.6-19.8)	0.180
SD of DBP, <sup>a</sup> mmHg	9.4(6.9-12.0)	10.1(7.6-13.4)	10.7(7.6-13.5)	0.010	9.9(7.3-12.6)	9.7(6.9-12.1)	10.5(7.6-13.5)	0.247
CV of SBP, <sup>a</sup> %	10.5(7.9-13.3)	11.1(8.4-14.4)	12.0(8.5-16.7)	0.005	10.9(8.5-14.2)	10.5(7.5-14.4)	11.6(8.4-14.6)	0.411
CV of DBP, <sup>a</sup> %	12.8(10.0-16.1)	13.9(11.1-17.8)	14.7(10.7-18.5)	0.003	14.3(10.7-16.9)	13.1(10.2-16.9)	13.9(10.9-18.1)	0.426

SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of



variation; SD: standard deviation.

<sup>a</sup>: Continuous variables with non normally distribution were expressed as median (interquartile range) and compared with Kruskal–Wallis test.

**Table 3.** Results of spearman correlation analysis between the degree of EPVS and ABPV

	EPVS in BG		EPVS in WM	
	r	P value	r	P value
24h				
SD of SBP	0.216	0.000	-0.013	0.762
SD of DBP	0.082	0.051	0.030	0.481
CV of SBP	0.137	0.001	-0.008	0.854
CV of DBP	0.123	0.003	-0.028	0.505
Daytime				
SD of SBP	0.205	0.000	-0.024	0.562
SD of DBP	0.065	0.120	0.031	0.459
CV of SBP	0.135	0.001	-0.023	0.585
CV of DBP	0.109	0.009	-0.017	0.679
Nighttime				
SD of SBP	0.229	0.000	0.020	0.637
SD of DBP	0.125	0.003	0.043	0.309
CV of SBP	0.136	0.001	0.027	0.521
CV of DBP	0.135	0.001	0.007	0.870

SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of variation; SD: standard deviation.

**Table 4.** Results of ordinal logistic regression analysis between ABPV and EPVS in BG

	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P

24h

SD of SBP	1.55 (1.32-1.83)	<0.001	1.48 (1.25-1.75)	<0.001	1.41 (1.19-1.68)	<0.001
CV of SBP	1.47 (1.19-1.83)	<0.001	1.48 (1.18-1.85)	0.001	1.60 (1.27-2.02)	<0.001
CV of DBP	1.59 (1.13-2.24)	0.008	1.69 (1.18-2.42)	0.004	1.81 (1.25-2.60)	0.001
Daytime						
SD of SBP	1.44 (1.25-1.67)	<0.001	1.39 (1.19-1.61)	<0.001	1.31 (1.12-1.54)	0.001
CV of SBP	1.32 (1.08-1.61)	0.006	1.32 (1.08-1.62)	0.008	1.43 (1.16-1.77)	0.001
CV of DBP	1.49 (1.10-2.04)	0.011	1.59 (1.15-2.19)	0.005	1.67 (1.21-2.31)	0.002
Nighttime						
SD of SBP	1.29 (1.15-1.46)	<0.001	1.25 (1.11-1.40)	<0.001	1.21 (1.07-1.37)	0.002
SD of DBP	1.39 (1.15-1.67)	<0.001	1.33 (1.11-1.61)	0.003	1.31 (1.12-1.54)	0.001
CV of SBP	1.27 (1.09-1.48)	0.002	1.26 (1.08-1.47)	0.003	1.31 (1.08-1.58)	0.006
CV of DBP	1.19 (1.04-1.36)	0.013	1.20 (1.04-1.37)	0.012	1.21 (1.05-1.39)	0.008

1 Results of ordinal regression analysis presented as OR per 5% increase in CV of  
 2 blood pressure and 5 mmHg in SD of blood pressure.

3 Model1: adjusted for age, smoking, alcohol, hypertension, stroke/TIA, BUN,  
 4 creatinine and using of anti-hypertensive drugs.

5 Model2: model 1 + Fazekas scale.

6 Model3: model 2 + the mean SBP or DBP during the same period.

## 7 DISCUSSION

8 In this study, we explored the relationship between ABPV and EPVS based on the  
 9 population who presented for physical examinations. Our data suggested that all of  
 10 the following metrics: SD of SBP, CV of SBP and CV of DBP during 24-hour,  
 11 daytime and nighttime and SD of DBP during nighttime were positively associated  
 12 with the degree of EPVS in BG. The association between the above ABPV metrics  
 13 and EPVS in BG were unchanged after adjusting for demographic confounders,  
 14 Fazekas scale and the mean SBP or DBP during the same period. Although there were  
 15 statistical differences in ABPV metrics during 24-hour and daytime among the three  
 16 subgroups stratified by EPVS severity in WM, there were no linear correlation  
 17 between ABPV and the degree of EPVS in WM. In addition, we found age, Fazekas  
 18 scale, hypertension, stroke/transient ischemic attack (TIA), levels of blood urea

nitrogen and creatinine were positively associated with the degree of EPVS in BG.

There were methodological strengths of our study. We recruited participants strictly according to inclusion and exclusion criteria to avoid selection bias. The patients with acute cerebrovascular and cardiovascular disorders were excluded to avoid the impact of the acute stroke, recent myocardial infarction or angina pectoris on blood pressure. The patients with a history of severe ischemic (the largest diameter of infarct size > 20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke were excluded because of difficulty and inaccurate assessment on EPVS. In addition, the assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments. We collected detailed information on vascular confounders, WMH, levels of blood urea nitrogen and creatinine, which are crucial to the interpretation of EPVS<sup>6, 20</sup>. So we think the reliability of the data is high. There were some limitations in our study. First, our study was based on a population who visited the hospital for physical exam in a single center and the cohort may not represent the general population. According to our observation, these people had a higher economic status than that of the general population in China, and some of them showed more symptoms of anxiety. But it's regrettable that we didn't assess the anxiety symptoms by the Hamilton Anxiety Rating Scale or assess the patients' education level. Second, this was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established. Third, all participants underwent 24-hour ABPM which could only show short-term ABPV. It has been demonstrated that the prognostic significance of BPV on vascular diseases is weaker for short-term than for long-term BPV<sup>21</sup>. Forth, the variables were compared among three categories and the type I error was probably elevated.

This is the first study to investigate the relationship between ABPV and EPVS. Previously, several studies investigated the relationship between EPVS and hypertension. In a prospective, multicenter, hospital-based study, Zhang CQ et al<sup>22</sup> found hypertension was associated with the severity of EPVS in WM, not in BG. Klarenbeek P et al<sup>23</sup> investigated the association between ABP levels and EPVS in

1 first-ever lacunar stroke patients. They found higher day systolic, day diastolic and  
2 24-hour diastolic BP levels were independently associated EPVS in BG, and no  
3 relation between ABP levels and EPVS in WM. We also analyzed the correlation  
4 between ABP levels and EPVS. We found ABP levels were associated with EPVS in  
5 BG, but not in WMH, which is consistent with Klarenbeek P et al.'s study. However,  
6 we found only SBP was positively related to higher degree of EPVS in BG in all  
7 periods, and no relation between DBP and EPVS, which are different from previous  
8 results. The different study population and different scoring methods of assessing  
9 EPVS may partly lead to the different results. Our data suggested that SD of SBP, CV  
10 of SBP and CV of DBP in all periods were positively associated with the degree of  
11 EPVS in BG, but not in WM. The present study couldn't explain the phenomenon.  
12 This may be caused by different pathogenesis of EPVS at the different locations<sup>22, 24,</sup>  
13 <sup>25</sup>. Previous studies have found the anatomical structure of EPVS located in BG and  
14 WM were different<sup>26</sup>. The arteries in the basal ganglia are surrounded by 2 distinct  
15 coats of leptomeninges separated by a perivascular space which is continuous with the  
16 perivascular space around arteries in the subarachnoid space. Whereas there are only  
17 single periarterial layer of leptomeninges surrounding the arteries in the cerebral  
18 cortex and they penetrate into the white matter. Drainage of interstitial fluid from the  
19 brain to cervical lymph nodes may mainly go along perivascular spaces in WM rather  
20 than in BG<sup>3, 27</sup>. In addition, the impact of age, hypertension on EPVS seems to be  
21 stronger for EPVS located in BG than for those located in WM<sup>24</sup>. Similarly, the  
22 association between EPVS and the load of WMH, taken as a marker of CSVD, also  
23 appears to be stronger in BG than in WM. Thus, their dilations may present  
24 differences in terms of risk factors as well as in mechanisms in BG and WM.  
25 However, the reason SBP is related differently in these two locations remains unclear  
26 because there are a very limited number of studies on mechanisms underlying dilation  
27 of perivascular spaces in BG and WM. Several studies have demonstrated higher  
28 ABPV increased the risk of neuroimaging features of CSVD, such as WMH and  
29 lacunar infarction<sup>14, 15</sup>. Our results found higher ABPV was independently associated  
30 with higher degree of EPVS in BG, which support the finding that EPVS in BG are a

1 separate marker of CSVD.  
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5 An increased permeability of the small vessel walls and blood brain barrier (BBB) are  
6  
7 considered to contribute to the development of EPVS, which has been reported to be  
8  
9 associated with damage of microvascular endothelial cells and their tight junctions<sup>1, 16,</sup>  
10  
11 <sup>28</sup>. Higher ABPV would lead to more mechanical stress on the wall vessel, endothelial  
12  
13 injury<sup>29</sup> and arterial stiffness<sup>30</sup>. Therefore, it is reasonable that high ABPV contribute  
14  
15 to the development of EPVS by damaging endothelial cells. Our results may remind  
16  
17 clinicians that they should pay attention to patients' ABPV and lower patients' ABPV  
18  
19 in their clinical practices. In the future, a prospective cohort study will help better  
20  
21 establish the relationship between ABPV and EPVS.

22 **CONCLUSION**

23  
24 SD of SBP, CV of SBP and CV of DBP during all periods and SD of DBP during  
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26 nighttime were positively associated with the degree of EPVS in BG. The association  
27  
28 was unchanged after adjusting for confounders. No relation was found between ABPV  
29  
30 and EPVS in WM. It is important for clinicians to reduce both patients' high blood  
31  
32 pressure levels and ABPV.

33 **Contributors** WH conceived and designed the experiments. SY, WQ, LY and HF  
34  
35 participated in the data collection. JY and YL participated in the analysis of the data.  
36  
37 SY drafted the manuscript. WH has given final approval of the version to be  
38  
39 published. All authors read and approved the final manuscript.

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44  
45 **Conflict of Interest** None declared.

46  
47 **Ethic approval** The study was approved by the Ethics Committee of Beijing  
48  
49 Chaoyang Hospital Affiliated to Capital Medical University and was performed in  
50  
51 accordance with the declaration of Helsinki.

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53  
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56 **Data sharing statement** We agreed to share our data on request.

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9 **Figure 1.** The ABPV metrics of subgroups stratified by EPVS severity in BG during  
10 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD  
11 of systolic blood pressure. (d) SD of diastolic blood pressure.

12 **Figure 2.** The ABPV metrics of subgroups stratified by EPVS severity in BG during  
13 daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD  
14 of systolic blood pressure. (d) SD of diastolic blood pressure.

15 **Figure 3.** The ABPV metrics of subgroups stratified by EPVS severity in BG during  
16 nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c)  
17 SD of systolic blood pressure. (d) SD of diastolic blood pressure.



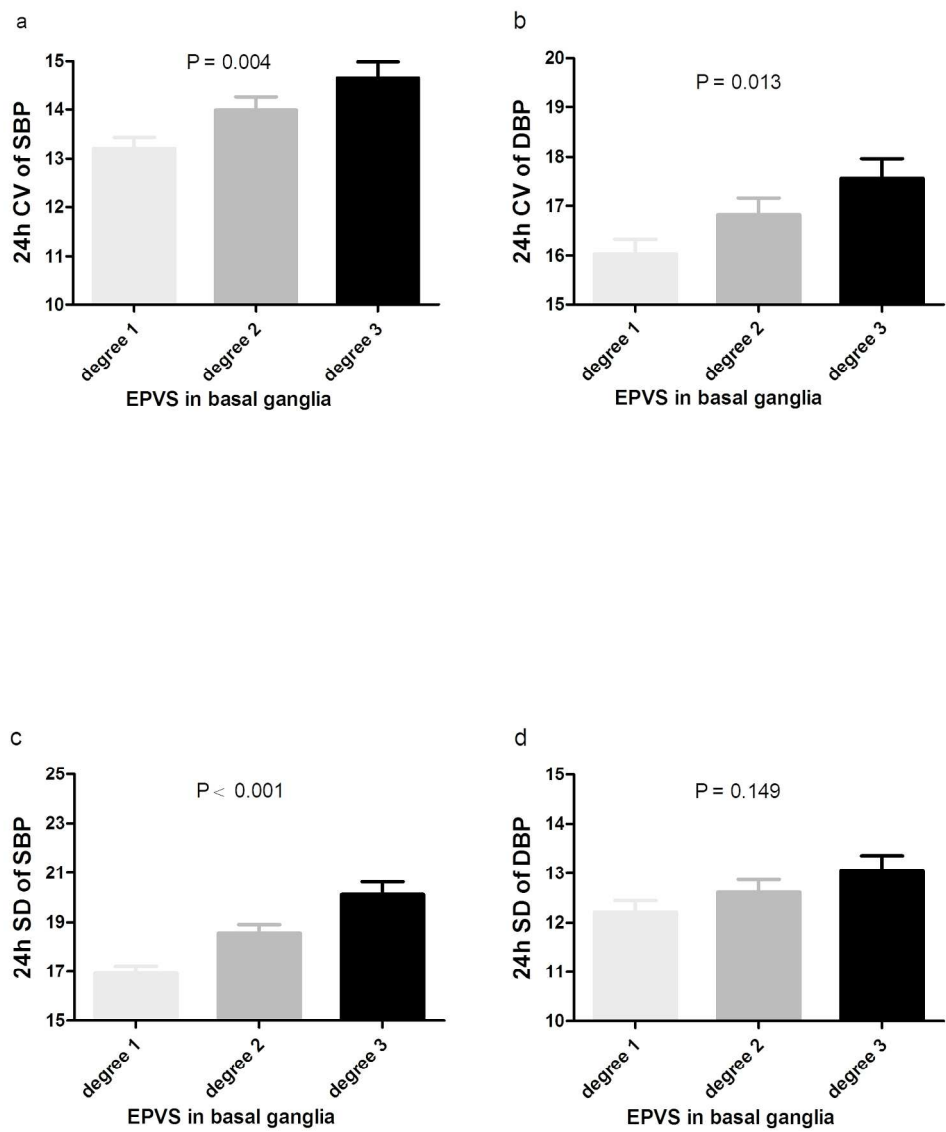


Figure 1. The ABPV metrics of subgroups stratified by EPVS severity in BG during 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

191x228mm (300 x 300 DPI)

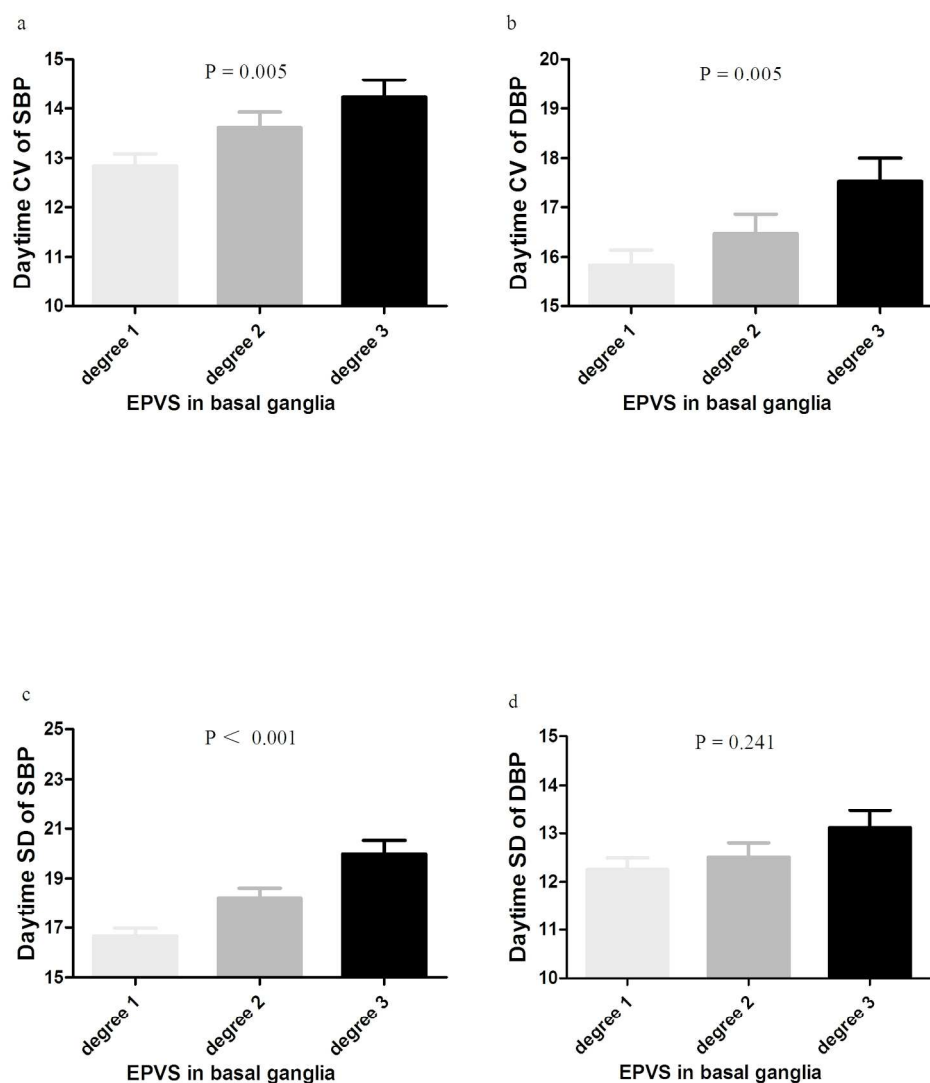


Figure 2. The ABPV metrics of subgroups stratified by EPVS severity in BG during daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

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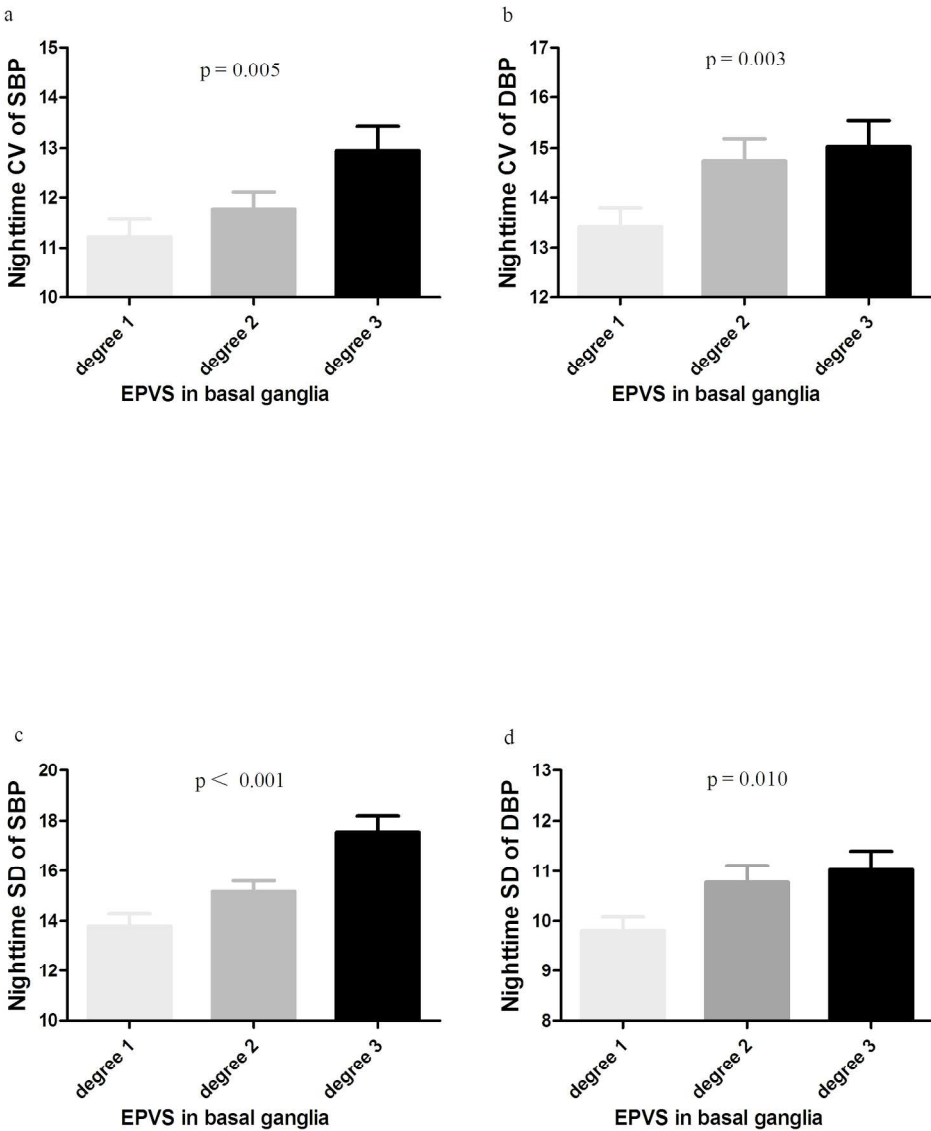


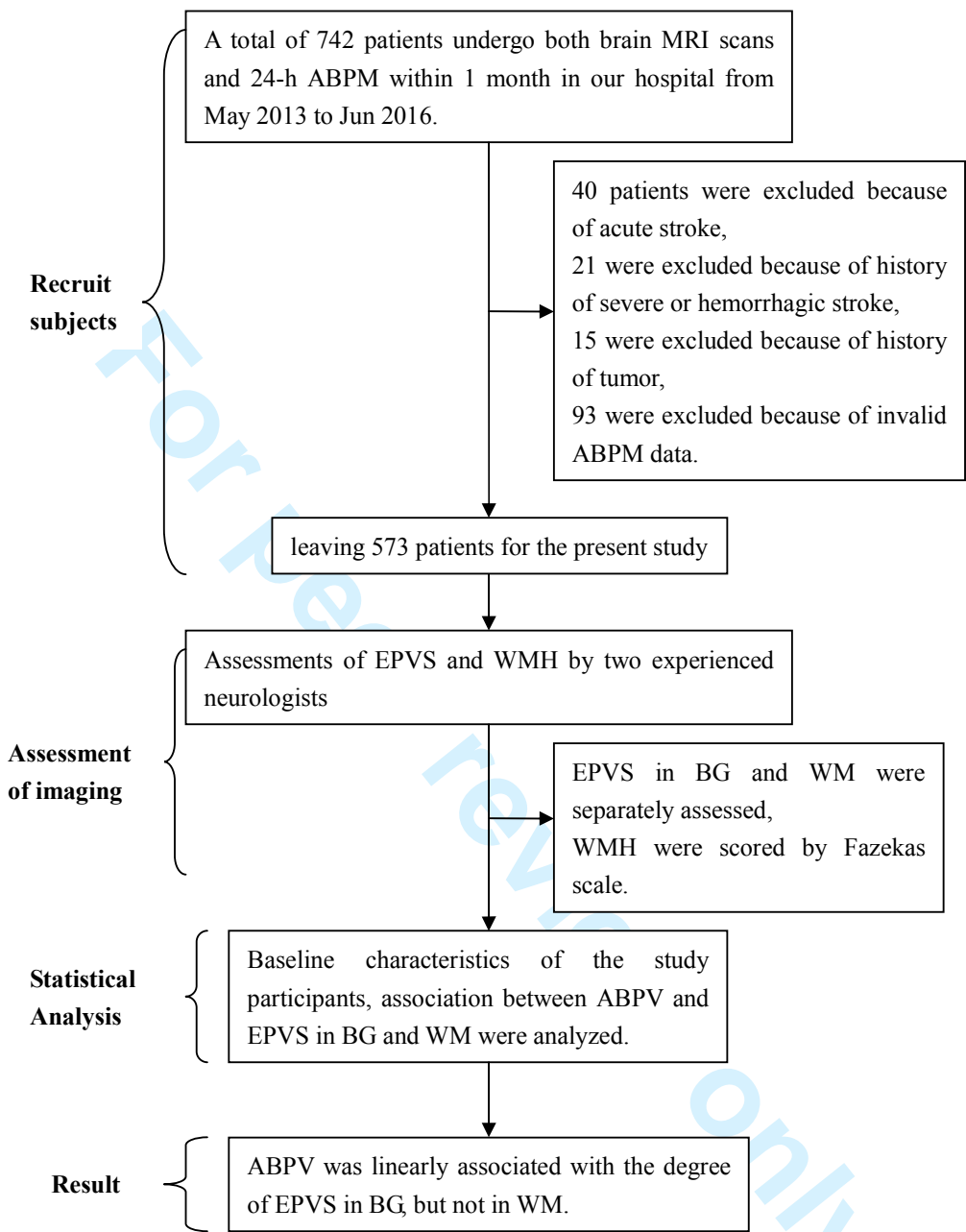
Figure 3. The ABPV metrics of subgroups stratified by EPVS severity in BG during nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

189x227mm (300 x 300 DPI)

The comparison of general clinical characteristics between the included and excluded participants

Characteristics	enrolled patients	excluded patients	P
n	573	169	-
Age, years	67.8±14.8	69.6±9.6	0.443
Sex, male (%)	355 (62.0)	101(59.8)	0.607
Current smoking (%)	162 (28.3)	55(32.5)	0.283
Current alcohol (%)	126 (22.0)	42(24.9)	0.435
Hypertension (%)	420 (73.3)	115(68.0)	0.181
Diabetes (%)	191 (33.3)	44(26.0)	0.073
coronary atherosclerosis disease (%)	140 (24.4)	35(20.7)	0.316
body mass index, kg/m <sup>2</sup>	25.6±3.5	25.1±3.0	0.160
Using of anti-hypertensive drugs (%)	342 (59.7)	99(58.6)	0.797

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ABPM, ambulatory blood pressure monitoring; EPVS, enlarged perivascular spaces; WMH, white matter hyperintensities; BG, basal ganglia; WM, white matter.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	P1 and 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	P2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	P4
Methods			
Study design	4	Present key elements of study design early in the paper	P4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	P4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P5-6
Bias	9	Describe any efforts to address potential sources of bias	P4 and 5

Study size	10	Explain how the study size was arrived at	P4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	P6
		(b) Describe any methods used to examine subgroups and interactions	P6
		(c) Explain how missing data were addressed	P6
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P6
		(b) Give reasons for non-participation at each stage	P6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P7
		(b) Indicate number of participants with missing data for each variable of interest	P7
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P6-12
		(b) Report category boundaries when continuous variables were categorized	

		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	P12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	P14-15
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P15

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).



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## The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study

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**1     The relationship between ambulatory blood pressure variability and**  
**2     enlarged perivascular spaces: a cross-sectional study**

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## Abstract

**Objectives:** Recent studies reported that 24-hour ambulatory blood pressure variability (ABPV) was associated with lacunar infarction and white matter hyperintensities (WMH). However, the relationship between ABPV and enlarged perivascular spaces (EPVS) hasn't been investigated. Thus, our study aimed to investigate whether ABPV is associated with EPVS by 24-hour ambulatory blood pressure monitoring (ABPM).

**Design:** We conducted this study as a cross-sectional study.

**Settings:** The study was based on patients who presented for physical examinations in our hospital from May 2013 to Jun 2016.

**Participants:** Patients with both brain MRI scans and 24-hour ABPM were included and patients with acute stroke, a history of severe stroke and some other severe diseases were excluded. A total of 573 Chinese patients were prospectively enrolled in this study.

**Primary and secondary outcome measures:** EPVS in basal ganglia (BG) and white matter (WM) were identified on MRI and classified into three categories by the severity. WMH were scored by Fazekas scale. Coefficient of variation (CV) and standard deviation (SD) were considered as metrics of ABPV. Spearman correlation analysis and ordinal logistic regression analysis were used to assess the relationship between ABPV and EPVS.

**Results:** There were statistical differences among the subgroups stratified by the severity of EPVS in BG in the following ABPV metrics: SD and CV of systolic blood pressure (SBP), CV of diastolic blood pressure (DBP) in 24-hour, daytime and nighttime and SD of DBP in nighttime. The above ABPV metrics were positively associated with the degree of EPVS. The association was unchanged after adjusting for confounders. Spearman correlation analysis showed ABPV wasn't related to the degree of EPVS in WM.

**Conclusion:** ABPV was independently associated with EPVS in BG after controlling for blood pressure, but not in WM. Pathogenesis of EPVS in BG and WM might be different.

**Keywords** cerebral small vessel disease, enlarged perivascular spaces, Virchow-Robin spaces, blood pressure variability, ambulatory blood pressure monitoring

**Strengths and limitations of this study**

- Assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments.
- Detailed information on some confounders crucial to the interpretation of EPVS was collected and ordinal logistic regression analysis was performed to determine the independency of association.
- The study was based on a population who presented to the hospital for physical exam in a single center and the cohort may not represent the general population.
- This was a cross-sectional study, and the causal relationship between ABPV and EPVS could not be established.

**INTRODUCTION**

Perivascular spaces, or Virchow-Robin spaces, are perivascular compartments surrounding the small penetrating cerebral vessels, serving as an important drainage system for interstitial fluids and solute in the brain<sup>1</sup>. They can dilate with accumulation of the interstitial fluids<sup>2, 3</sup>. Enlarged perivascular spaces (EPVS) appear as punctate or linear signal intensities similar to cerebrospinal fluids (CSF) on all MRI sequences in white matter (WM), basal ganglia (BG), hippocampus and brainstem<sup>4, 5</sup>. Recent studies indicated that EPVS were a magnetic resonance imaging (MRI) marker of cerebral small vessel diseases (CSVD) and were associated with other morphological features of CSVD such as white matter hyperintensities (WMH) and lacunes<sup>6, 7</sup>. Some studies found EPVS were associated with impaired cognitive function<sup>5</sup>, incident dementia<sup>8</sup> and sleep disorders<sup>9</sup>. Therefore, it is of clinical importance to understand the risk factors for EPVS and search for treatable options in the future.

24-hour ambulatory blood pressure monitoring (ABPM) is proven to be a more useful and scientific method to predict blood pressure-related brain damage than single

office blood pressure measurement<sup>10, 11</sup>. Ambulatory blood pressure variability (ABPV) could be well documented by 24-hour ABPM. Previous studies demonstrated higher ABPV increased the risk of cardiovascular events<sup>12, 13</sup>, WMH, lacunar infarction, and cognitive decline<sup>14, 15</sup>. WMH, lacunar infarction and EPVS are all neuroimaging features of CSVD and share some risk factors, such as age and hypertension<sup>16</sup>. However, the relationship between ABPV and EPVS has never been investigated. Thus in the present study, we aimed to investigate whether ABPV, which was reflected by 24-hour ABPM, was independently associated with EPVS.

## METHODS

### Study subjects

We conducted this study as a cross-sectional study. The inpatients for physical examinations in Medicine Department and Neurology Department of Beijing Chaoyang Hospital Affiliated to Capital Medical University were prospectively identified from May 2013 to Jun 2016. Some of them had a history of hypertension, diabetes mellitus, lacunar stroke or other risk factors for vascular diseases. They worried about the cerebrovascular diseases and wanted a well check up. They were screened according to our inclusion and exclusion criteria. The number of arriving patients during the study period, inclusion and exclusion criteria determined the sample size. Inclusion criteria were: (1) patients underwent both brain MRI scans and 24-hour ABPM within 1 month; (2) patients agreed to participate in our study and signed an informed consent. The following patients were excluded: (1) patients with acute stroke, Parkinson disease, dementia, severe traumatic or toxic or infectious brain injury, and brain tumor; (2) patients with severe heart disease, recent myocardial infarction or angina pectoris disorders, severe infections, severe nephrosis or liver disease, thrombotic diseases and tumor; (3) patients with history of severe ischemic (the largest diameter of infarct size > 20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke because of difficulty assessments on EPVS; (4) patients with invalid 24-hour ABPM data (The 24-h ABPM data were considered invalid if measurement times was < 70%, or < 1

1 measurement per hour during daytime, or < 6 in total during nighttime).

2 **Assessments of EPVS and WMH**

3 The neurological image examinations were performed in Radiology Department of  
4 our hospital. MR images were acquired on a 3.0 T MR scanner (Siemens, Erlangen,  
5 Germany).

6 EPVS were defined as CSF-like signal intensity lesions of round, ovoid, or linear  
7 shape of < 3mm and located in areas supplied by perforating arteries<sup>6, 17</sup>. We  
8 distinguished lacune from EPVS by their larger size (> 3mm), spheroid shape and  
9 surrounding hyperintensities on FLAIR. WMH were defined as hyperintense signals  
10 on T2-weighted and FLAIR and decreased signal intensities on T1-weighted MR  
11 imaging.

12 EPVS in BG and WM were separately assessed according to the scales which were  
13 used in other studies<sup>18</sup>. In BG, EPVS were rated according to the number in the slice  
14 containing the maximum amount of EPVS. The grades of EPVS were rated as  
15 following: grade 1: < 5 EPVS, grade 2: 5 to 10 EPVS, grade 3: 10 to 20 EPVS, and  
16 grade 4: > 20 EPVS. In WM, EPVS were scored as follows: grade 1: <10 EPVS in  
17 total WM, grade 2: >10 in total WM and <10 in the slice containing the maximum  
18 number of EPVS, grade 3: 10 to 20 EPVS in the slice containing the maximum  
19 number of EPVS, grade 4: > 20 in the slice containing the maximum number of EPVS.  
20 We classified EPVS into three categories: degree 1 = grade 1; degree 2 = grade 2;  
21 degree 3 = grade 3 and 4.

22 WMH were scored by Fazekas scale. The detailed description of assessments has  
23 been previously published<sup>19</sup>. Periventricular and deep WMH were evaluated  
24 separately and then added together as Fazekas scores.

25 The intrarater agreement for the rating of EPVS and WMH was assessed on a random  
26 sample of 100 individuals with a month interval between the first and second readings.  
27 Assessments of EPVS and WMH were performed by two experienced neurologists  
28 blinded to clinical information to avoid bias. Random scans of 100 individuals were  
29 independently examined by the two experienced neurologists blinded to each other's  
30 readings. The *k* statistics of intrarater and interrater agreement was 0.80 or above,

1 indicating good reliability. Disagreement was resolved by discussing with other  
2 co-authors.

### 3 **24-hour ambulatory blood pressure monitoring**

4 24-hour ABPM was performed using an automated system (FB-250; Fukuda Denshi,  
5 Tokyo, Japan). BP was measured every 30 minutes during the daytime (8:00 AM to  
6 11:00 PM) and every 60 minutes during the nighttime (11:00 PM to 8:00 AM). We  
7 excluded a 2-hour transition period around the reported rising and retiring times. The  
8 mean systolic blood pressure (SBP), diastolic blood pressure (DBP), coefficient of  
9 variation (CV) and standard deviation (SD) of SBP and DBP during 24-hour, daytime,  
10 and nighttime were collected. The CV value was defined as the ratio between the SD  
11 and the mean SBP or DBP at the same periods. SD and CV were considered as  
12 metrics of BPV in this study. Patients continued taking their previous medications,  
13 and we registered the use of anti-hypertension drugs.

### 14 **Statistical analysis**

15 Continuous variables were summarized as mean values  $\pm$  standard deviation (SD) or  
16 median (interquartile range) according to whether its distribution conformed to a  
17 normal distribution. Analysis of variance (ANOVA) was used for comparison of  
18 continuous variables with both normal distribution and homogeneity of variance,  
19 whereas were compared with Kruskal–Wallis test as appropriate. Categorical  
20 variables were presented as absolute numbers and percentages. Chi-squared test was  
21 used for comparison of categorical variables. Spearman correlation analysis was used  
22 to calculate the association between ABPV and the severity of EPVS. The  
23 proportional odds assumption was met, thus ordinal logistic regression analysis was  
24 performed to determine whether the ABPV was independently associated with EPVS  
25 after adjusting for demographic confounders (model 1), Fazekas scale (model 2) and  
26 the mean SBP or DBP during the same period (model 3). The results were based on  
27 valid data; missing data were excluded. Analyses were performed with Statistical  
28 Package for Social Sciences (SPSS version21.0), and statistical significance was  
29 accepted at the  $p < 0.05$ .

### 30 **RESULTS**

1       **Baseline characteristics of the study participants**

2       742 patients underwent both brain MRI scans and 24-hour ABPM within 1 month in  
3       the Medicine Department or Neurology Department of our hospital from May 2013 to  
4       Jun 2016. 40 patients were excluded because of acute stroke, 21 were excluded  
5       because of history of severe or hemorrhagic stroke, 15 were excluded because of a  
6       history of tumor and 93 were excluded because of invalid ABPM data, leaving 573  
7       patients enrolled in the present study. None of them had missing data. There were no  
8       statistical differences ( $P>0.05$ ) in age, body mass index, proportion of male, current  
9       smoking, current alcohol, diabetes, hypertension, coronary artery atherosclerosis  
10      disease and using of anti-hypertensive drugs between the excluded subjects and the  
11      final group (Supplementary file). Table 1 showed the characteristics of all enrolled  
12      subjects and subgroups stratified by the degree of EPVS in different brain regions.  
13      Age, Fazekas scale, proportion of hypertension and stroke/TIA, levels of blood urea  
14      nitrogen and creatinine increased with the degree of EPVS in BG increasing. There  
15      were statistical differences in age, Fazekas scale and proportion of coronary artery  
16      atherosclerosis disease (CAD) among subgroups based on the degree of EPVS in  
17      WM.

18      **Table 1.** General characteristics of all enrolled subjects and each EPVS category  
19      stratified by the severity of EPVS

Characteristics	All patients	EPVS in basal ganglia			EPVS in white matter		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3
n (%)	573	244 (42.6%)	179 (31.2%)	150 (26.2%)	200 (34.9%)	207 (36.1%)	166 (29.0%)
Age, <sup>a</sup> years	69(55-81)	58(51-74)**	68(57-80)**	80(73-85)**	75(57-83)**	66(55-78)**	66(54-80)**
Sex, male (%)	355 (62.0)	143 (58.6)	108 (60.3)	104 (69.3)	115 (57.5)	128 (61.8)	112 (67.5)
Current smoking (%)	162 (28.3)	83 (34.0)*	61(34.1)*	18(12.0)*	52 (26.0)	60 (29.0)	50 (30.1)
Current alcohol (%)	126 (22.0)	62 (25.4)*	45 (25.1)*	19 (12.7)*	36 (18.0)	50 (24.2)	40 (24.1)
Hypertension (%)	420 (73.3)	170 (69.7)*	122 (68.2)*	128 (85.3)*	150 (75.0)	145 (70.5)	125 (74.7)
Diabetes (%)	191 (33.3)	78 (32.0)	59 (33.0)	54 (36.0)	71 (35.5)	62 (30.0)	58 (34.9)
CAD (%)	140 (24.4)	48 (19.7)	48 (26.8)	44 (29.3)	61 (30.5) *	45 (21.7) *	34 (20.5) *



Stroke or TIA (%)	125 (21.8)	40 (16.4)**	33 (18.4)**	52 (34.7)**	49 (24.5)	39 (18.8)	37 (22.2)
BMI, <sup>b</sup> kg/m <sup>2</sup>	25.6±3.5	25.6±3.4	25.3±3.5	25.8±3.5	25.8±3.4	25.4±3.5	25.5±3.5
HDL, <sup>a</sup> mmol/L	1.16(1.00-1.38)	1.15(0.99-1.37)	1.17(0.98-1.41)	1.17(1.00-1.32)	1.17(1.00-1.38)	1.15(0.98-1.37)	1.15(0.99-1.34)
LDL, <sup>a</sup> mmol/L	2.40(1.90-2.94)	2.42(1.96-3.00)	2.47(1.88-2.93)	2.20(1.79-2.91)	2.32(1.88-2.94)	2.29(1.81-2.90)	2.51(2.00-3.00)
HbA1c, <sup>a</sup> %	6.0(5.7-6.7)	6.0(5.7-6.7)	6.0(5.7-6.7)	6.1(5.7-6.7)	6.1(5.7-6.8)	6.0(5.7-6.6)	6.0(5.7-6.8)
BUN, <sup>a</sup> mmol/L	5.46(4.46-6.70)	5.18(4.34-6.34)**	5.36(4.32-6.59)**	5.97(4.82-7.42)**	5.50(4.55-7.02)	5.39(4.36-6.39)	5.42(4.50-6.81)
Creatinine, <sup>a</sup> umol/L	74.2(62.8-89.2)	70.2(59.7-84.6)**	74.5(63.7-89.6)**	81.9(66.4-94.1)**	77.0(62.8-92.1)	72.5(61.5-87.0)	74.0(62.9-89.1)
Fazekas scale <sup>a</sup>	3(2-5)	2(1-3)**	3(2-4)**	5(4-6)**	3(2-6)**	2(2-4)**	3(2-4)**
Using of anti-hypertensive drugs	342 (59.7)	130 (53.3) *	96 (53.6) *	116 (77.3) *	129 (64.5)	114 (55.1)	99 (59.6)
(%)							
Class of anti-hypertensive drugs							
Dihydropyridinic CCB (%)	226 (39.4)	74 (30.3)	67 (37.4)	63 (42.0)	69 (34.5)	79 (38.2)	55 (33.1)
ACEI (%)	26 (4.5)	11 (4.5)	6 (3.4)	9 (6.0)	8 (4.0)	9 (4.3)	9 (5.7)
ARB (%)	160 (27.9)	70 (28.7)	46 (25.7)	44 (29.3)	69 (34.5) *	52 (25.1) *	39 (23.5) *
β-Blockers (%)	96 (16.8)	34 (13.9)	28 (15.6)	34 (22.7)	40 (20.0)	31 (15.0)	25 (15.1)
Nonloop diuretics (%)	39 (6.8)	20 (8.2)	12 (6.7)	7 (4.7)	16 (8.0)	13 (6.3)	10 (6.0)

1 EPVS, enlarged perivascular spaces; BMI, body mass index; CAD, coronary artery  
2 atherosclerosis disease; TIA, transient ischemic attack; HDL, high-density lipoprotein;  
3 LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen,  
4 CCB, calcium-channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB,  
5 angiotensin receptor blocker. \*  $p < 0.05$ , \* \*  $p < 0.01$ .

6 <sup>a</sup>: Continuous variables with non normally distribution were expressed as median  
7 (interquartile range) and compared with Kruskal–Wallis test. <sup>b</sup>: Continuous variables  
8 with normal distribution were expressed as mean values ± standard deviation, but with  
9 heterogeneity of variance, thus were compared with Kruskal–Wallis test.

10 Ambulatory blood pressure levels for each EPVS category were presented in Table 2.  
11 There were statistical differences in the mean SBP during 24-hour, daytime, and  
12 nighttime among the categories stratified by the degree of EPVS in BG. The results of  
13 spearman correlation analysis showed SBP was positively related to higher degree of

EPVS in BG during all periods (SBP of 24-hour:  $r=0.23$ ,  $p < 0.01$ ; SBP of daytime:  $r=0.25$ ,  $p < 0.01$ ; SBP of nighttime:  $r=0.30$ ,  $p < 0.01$ ). The mean DBP of daytime and nighttime increased with the degree of EPVS in WMH increasing. However, the results of spearman correlation analysis showed that DBP levels were not associated with higher numbers of EPVS in WM ( $p > 0.05$ ).

**Table 2.** Ambulatory blood pressure levels of all enrolled subjects and each EPVS category stratified by the severity of EPVS

Characteristics	All patients	EPVS in basal ganglia			EPVS in white matter		
		Degree 1	Degree 2	Degree 3	Degree 1	Degree 2	Degree 3
24-hour							
SBP, <sup>a,b</sup> mmHg	132(121-143)	127(117-138)**	133(124-143)**	136(127-148)**	133±16.5	132±17.1	132.9±15.4
DBP, <sup>b</sup> mmHg	76±9.6	77±9.5	76±10.0	75±9.1	75±9.5*	76±9.6*	77±9.6*
Daytime							
SBP, <sup>a,b</sup> mmHg	134(123-145)	129(118-141)**	135(126-144)**	140(130-150)**	135±16.6	134±17.6	135±15.3
DBP, <sup>b</sup> mmHg	77±10.0	77±10.0*	77±10.3*	75±9.5*	75±9.9*	77±10.1*	78±9.9*
Nighttime							
SBP, <sup>a</sup> mmHg	126(116-142)	120(110-134)**	131(118-142)**	135(123-149)**	127(115-144)	124(113-140)	128(117-142)
DBP, <sup>a</sup> mmHg	73(66-80)	74(66-81)	73(66-81)	73(67-80)	71(65-79)	73(66-80)	75(68-82)

EPVS, enlarged perivascular spaces; SBP, systolic blood pressure; DBP, diastolic blood pressure. \*  $p < 0.05$ , \* \*  $p < 0.01$

<sup>a</sup>: Continuous variables with non normally distribution were expressed as median (interquartile range) and compared with Kruskal–Wallis test. <sup>b</sup>: Continuous variables with normal distribution were expressed as mean values ± standard deviation, but with heterogeneity of variance, thus were compared with Kruskal–Wallis test.

**Association between ABPV and EPVS in BG**

SD and CV of ambulatory blood pressure in different categories stratified by the degree of EPVS in BG were presented in Table 3. There were statistical differences ( $p < 0.05$ ) among the three subgroups stratified by the severity of EPVS in all of the following BPV metrics: SD and CV of SBP, CV of DBP during 24-hour, daytime and

nighttime and SD of DBP during nighttime. These metrics gradually increased with the degree of EPVS increasing (Fig 1-3). The results of spearman correlation analysis demonstrated these metrics were positively associated with the degree of EPVS in BG ( $r > 0$ ,  $P < 0.05$ ). The association between ABPV and EPVS were unchanged even after adjusting for demographic confounders (model 1), Fazekas scale (model 2) and the mean SBP or DBP during the same period (model 3), which indicated that the ABPV were independently associated with EPVS in BG. The results of ordinal logistic regression analysis were presented in Table 4.

### Association between ABPV and EPVS in WM

SD and CV of ambulatory blood pressure in different categories stratified by degree of EPVS in WM were also presented in Table 3. There were statistical differences ( $p < 0.05$ ) in SD of SBP, CV of SBP, SD of DBP and CV of DBP during 24-hour and daytime among the three categories. However, there were not linear trend among the three subgroups. The results of spearman correlation analysis showed there were no linear correlation between these metrics and the degree of EPVS in WM ( $P > 0.05$ ).

**Table 3.** Results of ABPV in all subjects and subgroups stratified by the severity of EPVS

	EPVS in BG				EPVS in WM			
	Degree 1	Degree 2	Degree 3	P	Degree 1	Degree 2	Degree 3	P
24-hour								
SD of SBP, <sup>a</sup> mmHg	16.6(13.8-20.2)	18.1(15.1-21.5)	18.8(15.5-23.9)	<0.001	18.2(14.7-22.8)	16.9(13.7-20.2)	17.7(15.0-21.7)	0.004
SD of DBP, <sup>a</sup> mmHg	11.8(9.8-14.3)	12.2(10.1-15.2)	12.5(10.1-15.3)	0.149	12.7(10.1-14.5)	11.4(9.4-14.1)	12.7(10.7-15.5)	0.001
CV of SBP, <sup>a</sup> %	12.9(10.4-15.3)	13.6(11.4-16.2)	14.4(11.2-17.4)	0.004	13.6(11.3-16.5)	13.2(10.3-15.5)	13.5(11.5-16.5)	0.028
CV of DBP, <sup>a</sup> %	15.4(12.9-19.0)	16.1(13.5-19.9)	17.3(13.8-20.2)	0.013	17.1(13.9-19.8)	15.0(12.4-18.4)	16.6(13.8-19.9)	0.001
Daytime								
SD of SBP, <sup>a</sup> mmHg	16.2(13.2-19.8)	17.1(14.2-21.5)	18.7(14.8-25.0)	<0.001	18.2(14.1-22.6)	16.3(13.2-19.7)	17.2(14.3-22.6)	0.004
SD of DBP, <sup>a</sup> mmHg	11.7(9.6-14.8)	11.8(9.5-15.0)	12.7(9.8-15.7)	0.241	12.2(9.7-15.3)	11.3(8.8-13.6)	12.6(10.2-16.0)	0.001

CV of SBP, <sup>a</sup> %	12.2(10.1-15.1)	12.9(10.8-16.1)	13.9(10.8-17.5)	0.005	13.3(10.6-16.7)	12.3(9.8-15.1)	13.1(10.5-16.6)	0.016
CV of DBP, <sup>a</sup> %	15.3(12.2-19.4)	15.1(12.7-20.5)	17.1(13.5-20.4)	0.024	16.4(13.3-20.3)	14.8(11.7-19.1)	16.3(13.2-20.4)	0.002
Nighttime								
SD of SBP, <sup>a</sup> mmHg	12.5(9.5-16.4)	14.8(11.0-19.0)	16.5(11.3-22.6)	<0.001	13.5(10.9-18.6)	13.4(9.8-18.9)	15.2(10.6-19.8)	0.180
SD of DBP, <sup>a</sup> mmHg	9.4(6.9-12.0)	10.1(7.6-13.4)	10.7(7.6-13.5)	0.010	9.9(7.3-12.6)	9.7(6.9-12.1)	10.5(7.6-13.5)	0.247
CV of SBP, <sup>a</sup> %	10.5(7.9-13.3)	11.1(8.4-14.4)	12.0(8.5-16.7)	0.005	10.9(8.5-14.2)	10.5(7.5-14.4)	11.6(8.4-14.6)	0.411
CV of DBP, <sup>a</sup> %	12.8(10.0-16.1)	13.9(11.1-17.8)	14.7(10.7-18.5)	0.003	14.3(10.7-16.9)	13.1(10.2-16.9)	13.9(10.9-18.1)	0.426

1 SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of  
2 variation; SD: standard deviation.

3 <sup>a</sup>: Continuous variables with non normally distribution were expressed as median  
4 (interquartile range) and compared with Kruskal–Wallis test.

5 **Table 4.** Results of ordinal logistic regression analysis between ABPV and EPVS in  
6 BG

	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
24h						
SD of SBP	1.55 (1.32-1.83)	<0.001	1.48 (1.25-1.75)	<0.001	1.41 (1.19-1.68)	<0.001
CV of SBP	1.47 (1.19-1.83)	<0.001	1.48 (1.18-1.85)	0.001	1.60 (1.27-2.02)	<0.001
CV of DBP	1.59 (1.13-2.24)	0.008	1.69 (1.18-2.42)	0.004	1.81 (1.25-2.60)	0.001
Daytime						
SD of SBP	1.44 (1.25-1.67)	<0.001	1.39 (1.19-1.61)	<0.001	1.31 (1.12-1.54)	0.001
CV of SBP	1.32 (1.08-1.61)	0.006	1.32 (1.08-1.62)	0.008	1.43 (1.16-1.77)	0.001
CV of DBP	1.49 (1.10-2.04)	0.011	1.59 (1.15-2.19)	0.005	1.67 (1.21-2.31)	0.002
Nighttime						
SD of SBP	1.29 (1.15-1.46)	<0.001	1.25 (1.11-1.40)	<0.001	1.21 (1.07-1.37)	0.002
SD of DBP	1.39 (1.15-1.67)	<0.001	1.33 (1.11-1.61)	0.003	1.31 (1.12-1.54)	0.001
CV of SBP	1.27 (1.09-1.48)	0.002	1.26 (1.08-1.47)	0.003	1.31 (1.08-1.58)	0.006

CV of DBP	1.19 (1.04-1.36)	0.013	1.20 (1.04-1.37)	0.012	1.21 (1.05-1.39)	0.008
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Results of ordinal regression analysis presented as OR per 5% increase in CV of blood pressure and 5 mmHg in SD of blood pressure.

Model1: adjusted for age, smoking, alcohol, hypertension, stroke/TIA, BUN, creatinine and using of anti-hypertensive drugs.

Model2: model 1 + Fazekas scale.

Model3: model 2 + the mean SBP or DBP during the same period.

## DISCUSSION

In this study, we explored the relationship between ABPV and EPVS based on the population who presented for physical examinations. Our data suggested that all of the following metrics: SD of SBP, CV of SBP and CV of DBP during 24-hour, daytime and nighttime and SD of DBP during nighttime were positively associated with the degree of EPVS in BG. The association between the above ABPV metrics and EPVS in BG were unchanged after adjusting for demographic confounders, Fazekas scale and the mean SBP or DBP during the same period. Although there were statistical differences in ABPV metrics during 24-hour and daytime among the three subgroups stratified by EPVS severity in WM, there were no linear correlation between ABPV and the degree of EPVS in WM. In addition, we found age, Fazekas scale, hypertension, stroke/transient ischemic attack (TIA), levels of blood urea nitrogen and creatinine were positively associated with the degree of EPVS in BG.

There were methodological strengths of our study. We recruited participants strictly according to inclusion and exclusion criteria to avoid selection bias. The patients with acute cerebrovascular and cardiovascular disorders were excluded to avoid the impact of the acute stroke, recent myocardial infarction or angina pectoris on blood pressure.

The patients with a history of severe ischemic (the largest diameter of infarct size > 20mm on diffusion-weighted imaging and fluid attenuated inversion recovery) or hemorrhagic stroke were excluded because of difficulty and inaccurate assessment on EPVS. In addition, the assessments of EPVS and WMH were performed by two experienced neurologists blinded to clinical information and disagreements were resolved by consensus, which ensure the accuracy of the assessments. We collected

1 detailed information on vascular confounders, WMH, levels of blood urea nitrogen  
2 and creatinine, which are crucial to the interpretation of EPVS<sup>6, 20</sup>. So we think the  
3 reliability of the data is high. There were some limitations in our study. First, our  
4 study was based on a population who visited the hospital for physical exam in a single  
5 center and the cohort may not represent the general population. According to our  
6 observation, these people had a higher economic status than that of the general  
7 population in China, and some of them showed more symptoms of anxiety. But it's  
8 regrettable that we didn't assess the anxiety symptoms by the Hamilton Anxiety  
9 Rating Scale or assess the patients' education level. Second, this was a cross-sectional  
10 study, and the causal relationship between ABPV and EPVS could not be established.  
11 Third, all participants underwent 24-hour ABPM which could only show short-term  
12 ABPV. It has been demonstrated that the prognostic significance of BPV on vascular  
13 diseases is weaker for short-term than for long-term BPV<sup>21</sup>. Forth, the variables were  
14 compared among three categories and the type I error was probably elevated.  
15 This is the first study to investigate the relationship between ABPV and EPVS.  
16 Previously, several studies investigated the relationship between EPVS and  
17 hypertension. In a prospective, multicenter, hospital-based study, Zhang CQ et al<sup>22</sup>  
18 found hypertension was associated with the severity of EPVS in WM, not in BG.  
19 Klarenbeek P et al<sup>23</sup> investigated the association between ABP levels and EPVS in  
20 first-ever lacunar stroke patients. They found higher day systolic, day diastolic and  
21 24-hour diastolic BP levels were independently associated EPVS in BG, and no  
22 relation between ABP levels and EPVS in WM. We also analyzed the correlation  
23 between ABP levels and EPVS. We found ABP levels were associated with EPVS in  
24 BG, but not in WMH, which is consistent with Klarenbeek P et al.'s study. However,  
25 we found only SBP was positively related to higher degree of EPVS in BG in all  
26 periods, and no relation between DBP and EPVS, which are different from previous  
27 results. The different study population and different scoring methods of assessing  
28 EPVS may partly lead to the different results. Our data suggested that SD of SBP, CV  
29 of SBP and CV of DBP in all periods were positively associated with the degree of  
30 EPVS in BG, but not in WM. The present study couldn't explain the phenomenon.

This may be caused by different pathogenesis of EPVS at the different locations<sup>22, 24, 25</sup>. Previous studies have found the anatomical structure of EPVS located in BG and WM were different<sup>26</sup>. The arteries in the basal ganglia are surrounded by 2 distinct coats of leptomeninges separated by a perivascular space which is continuous with the perivascular space around arteries in the subarachnoid space. Whereas there are only single periarterial layer of leptomeninges surrounding the arteries in the cerebral cortex and they penetrate into the white matter. Drainage of interstitial fluid from the brain to cervical lymph nodes may mainly go along perivascular spaces in WM rather than in BG<sup>3, 27</sup>. In addition, the impact of age, hypertension on EPVS seems to be stronger for EPVS located in BG than for those located in WM<sup>24</sup>. Similarly, the association between EPVS and the load of WMH, taken as a marker of CSVD, also appears to be stronger in BG than in WM. Thus, their dilations may present differences in terms of risk factors as well as in mechanisms in BG and WM. However, the reason SBP is related differently in these two locations remains unclear because there are a very limited number of studies on mechanisms underlying dilation of perivascular spaces in BG and WM. Several studies have demonstrated higher ABPV increased the risk of neuroimaging features of CSVD, such as WMH and lacunar infarction<sup>14, 15</sup>. Our results found higher ABPV was independently associated with higher degree of EPVS in BG, which support the finding that EPVS in BG are a separate marker of CSVD.

An increased permeability of the small vessel walls and blood brain barrier (BBB) are considered to contribute to the development of EPVS, which has been reported to be associated with damage of microvascular endothelial cells and their tight junctions<sup>1, 16, 28</sup>. Higher ABPV would lead to more mechanical stress on the wall vessel, endothelial injury<sup>29</sup> and arterial stiffness<sup>30</sup>. Therefore, it is reasonable that high ABPV contribute to the development of EPVS by damaging endothelial cells. Our results may remind clinicians that they should pay attention to patients' ABPV and lower patients' ABPV in their clinical practices. In the future, a prospective cohort study will help better establish the relationship between ABPV and EPVS.

## CONCLUSION



SD of SBP, CV of SBP and CV of DBP during all periods and SD of DBP during nighttime were positively associated with the degree of EPVS in BG. The association was unchanged after adjusting for confounders. No relation was found between ABPV and EPVS in WM. It is important for clinicians to reduce both patients' high blood pressure levels and ABPV.

**Contributors** WH conceived and designed the experiments. SY, WQ, LY and HF participated in the data collection. JY and YL participated in the analysis of the data. SY drafted the manuscript. WH has given final approval of the version to be published. All authors read and approved the final manuscript.

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**Conflict of Interest** None declared.

**Ethic approval** The study was approved by the Ethics Committee of Beijing Chaoyang Hospital Affiliated to Capital Medical University and was performed in accordance with the declaration of Helsinki.

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**Data sharing statement** We agree to share our data on request. Please contact the corresponding author for access to the data.

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39 **Figure 1.** The ABPV metrics of subgroups stratified by EPVS severity in BG during  
40 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD  
41 of systolic blood pressure. (d) SD of diastolic blood pressure.

42 **Figure 2.** The ABPV metrics of subgroups stratified by EPVS severity in BG during

1 daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD  
2 of systolic blood pressure. (d) SD of diastolic blood pressure.

3 **Figure 3.** The ABPV metrics of subgroups stratified by EPVS severity in BG during  
4 nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c)  
5 SD of systolic blood pressure. (d) SD of diastolic blood pressure.

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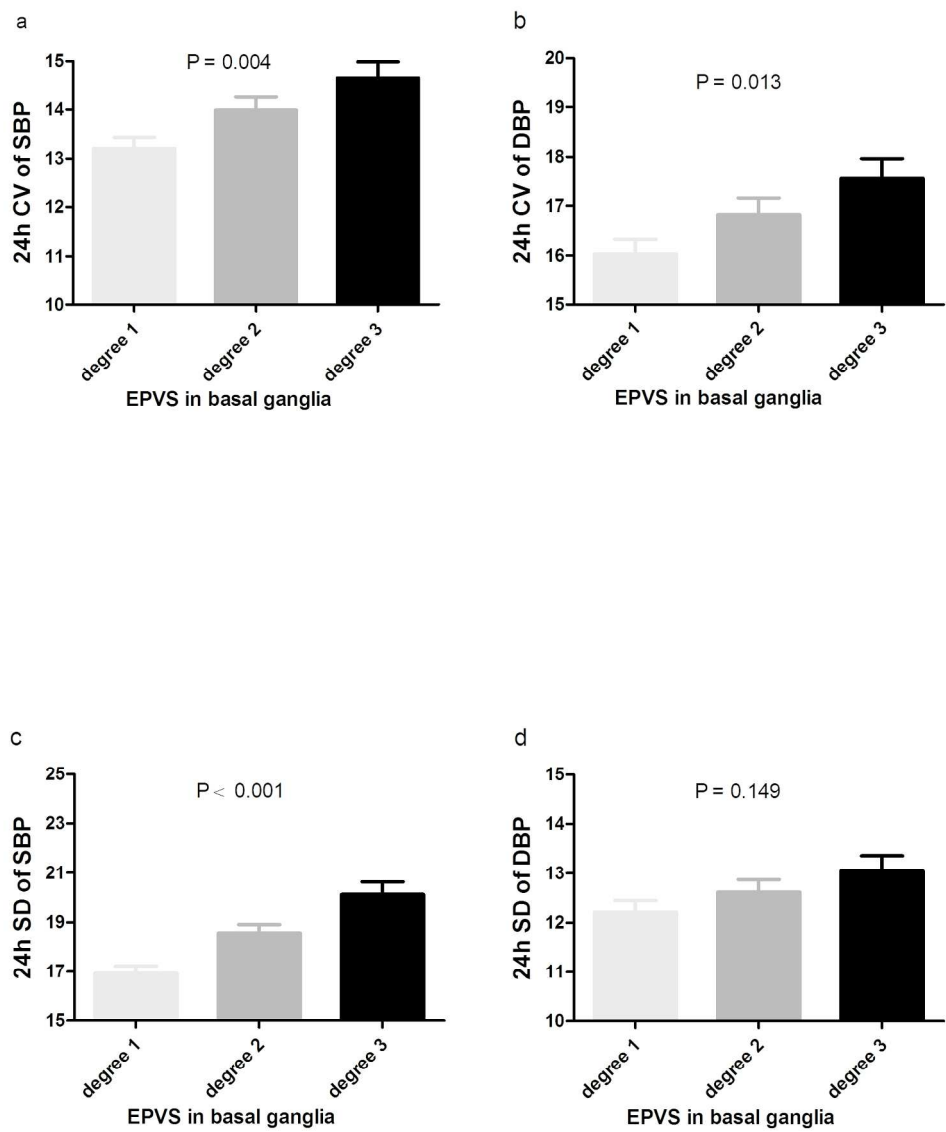


Figure 1. The ABPV metrics of subgroups stratified by EPVS severity in BG during 24-hour. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

191x228mm (300 x 300 DPI)

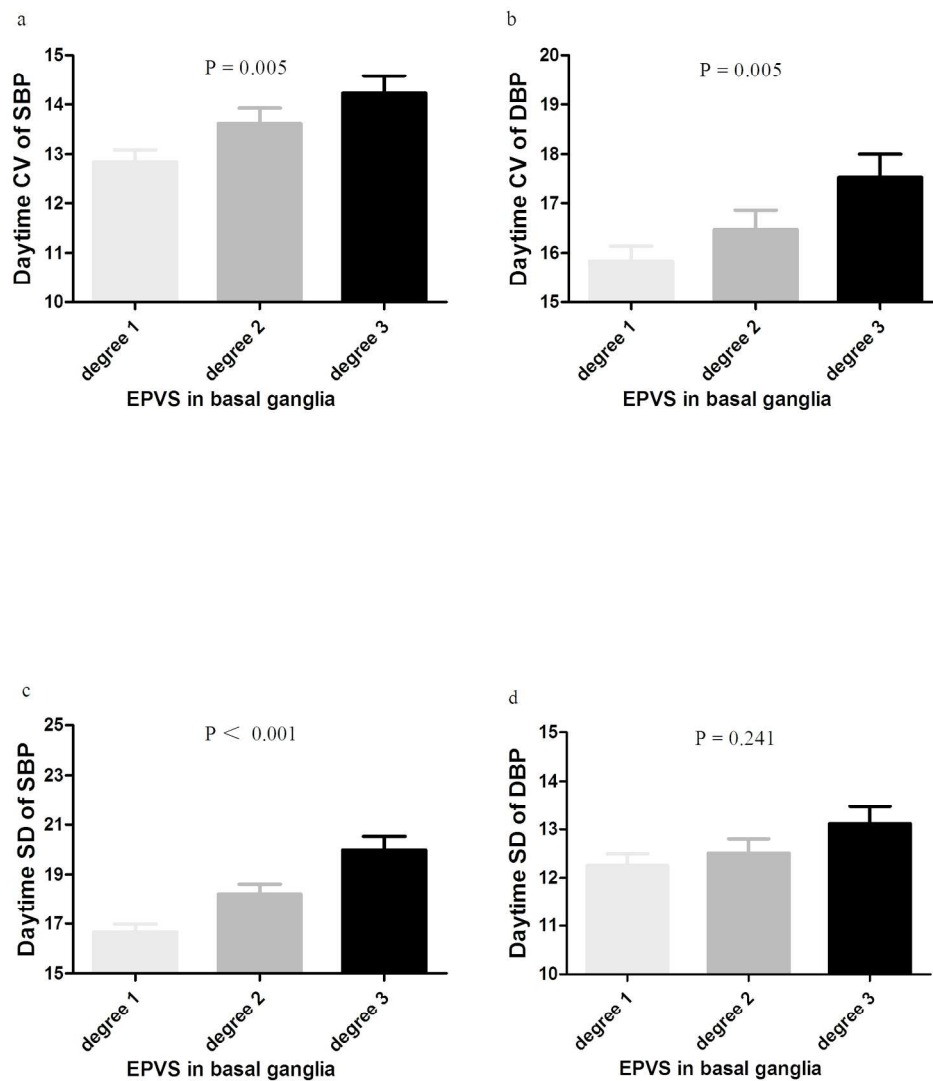


Figure 2. The ABPV metrics of subgroups stratified by EPVS severity in BG during daytime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

190x218mm (300 x 300 DPI)

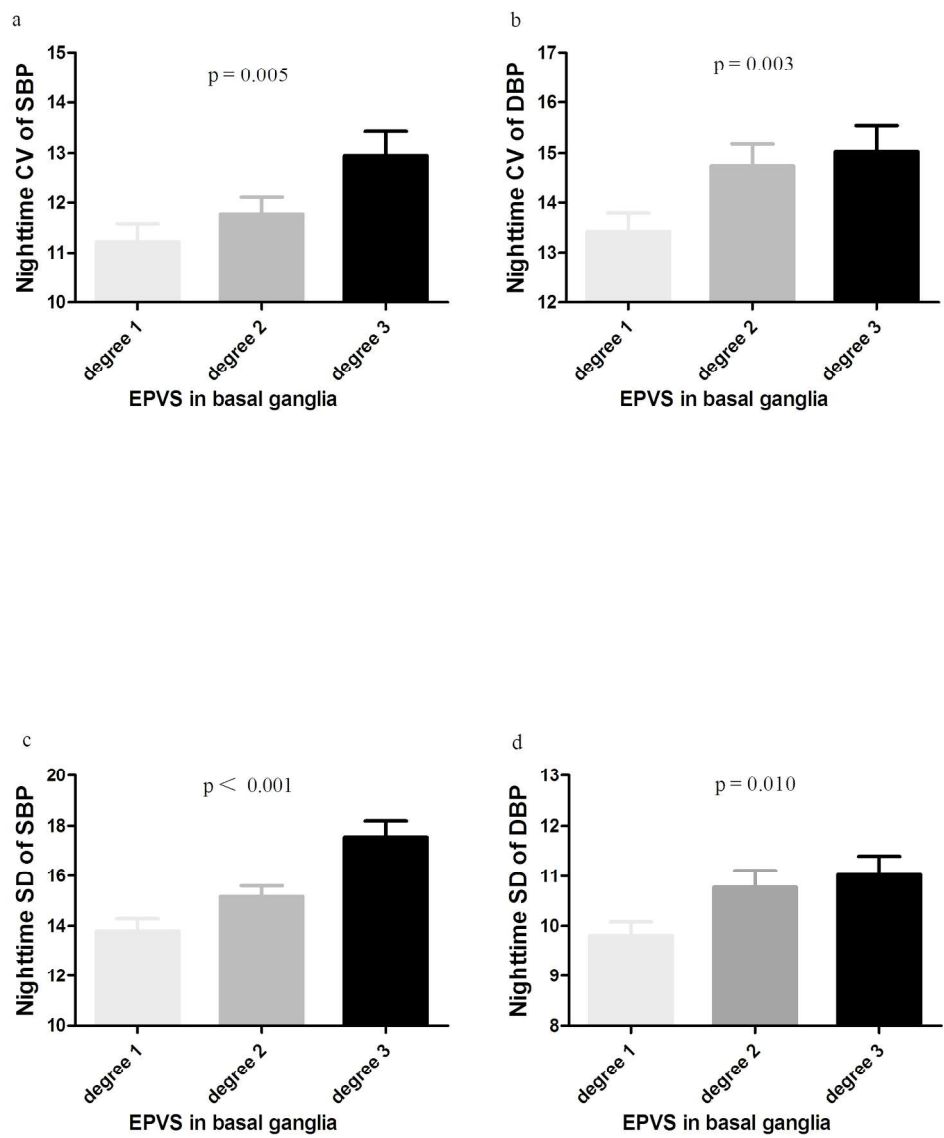


Figure 3. The ABPV metrics of subgroups stratified by EPVS severity in BG during nighttime. (a) CV of systolic blood pressure. (b) CV of diastolic blood pressure. (c) SD of systolic blood pressure. (d) SD of diastolic blood pressure.

189x227mm (300 x 300 DPI)

The comparison of general clinical characteristics between the included and excluded participants

Characteristics	enrolled patients	excluded patients	P
n	573	169	-
Age, years	67.8±14.8	69.6±9.6	0.443
Sex, male (%)	355 (62.0)	101(59.8)	0.607
Current smoking (%)	162 (28.3)	55(32.5)	0.283
Current alcohol (%)	126 (22.0)	42(24.9)	0.435
Hypertension (%)	420 (73.3)	115(68.0)	0.181
Diabetes (%)	191 (33.3)	44(26.0)	0.073
coronary atherosclerosis disease (%)	140 (24.4)	35(20.7)	0.316
body mass index, kg/m <sup>2</sup>	25.6±3.5	25.1±3.0	0.160
Using of anti-hypertensive drugs (%)	342 (59.7)	99(58.6)	0.797

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	P1 and 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	P2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	P4
Methods			
Study design	4	Present key elements of study design early in the paper	P4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	P4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P5-6
Bias	9	Describe any efforts to address potential sources of bias	P4 and 5



Study size	10	Explain how the study size was arrived at	P4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	P6
		(b) Describe any methods used to examine subgroups and interactions	P6
		(c) Explain how missing data were addressed	P6
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P6
		(b) Give reasons for non-participation at each stage	P6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P7
		(b) Indicate number of participants with missing data for each variable of interest	P7
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P6-12
		(b) Report category boundaries when continuous variables were categorized	

		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	P12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	P14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P15

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).